Archives of Neurology and Psychiatry

VOLUME 58 OCTOBER 1947 NUMBER 4

DISSEMINATED ENCEPHALOMYELITIS EXPERIMENTALLY PRODUCED BY THE USE OF HOMOLOGOUS ANTIGEN

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THE ACUTE disseminated encephalomyelitis that sometimes follows vaccination against rabies [1] or smallpox,[2] as well as the post-infectious encephalomyelitis following exanthematous diseases, bears such an apparently close relation to multiple sclerosis, Schilder's disease (progressive subcortical encephalopathy) and other demyelinating processes in the central nervous system that it has attracted the attention of numerous investigators in recent years. But it was in 1895 that Pierre Marie [3] first stressed the observation that multiple sclerosis frequently followed smallpox. The literature has been rather completely covered by Ferraro [4] and the reader is referred to him for a bibliography dealing with phases of the problem that are beyond the scope of the present experiments.

As long ago as 1898, while studying the toxic effects of tissues of other species, during his investigations on diphtheria and on rabies, Centanni [5] observed the untoward effects of saline suspensions of brain

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Read before the Boston Society of Psychiatry and Neurology, April 17, 1947.

A part of the expense of this investigation was defrayed by the Commonwealth Fund.

From the Department of Neuropathology and the Robert W. Lovett Fund for the Study of Crippling Disease, Harvard Medical School, and the Neuropathology Laboratory, Massachusetts General Hospital.

1. Bassoe, P., and Grinker, R. R.: Human Rabies and Rabies Vaccine Encephalomyelitis: Clinicopathologic Study, Arch. Neurol. & Psychiat. **23**:1138 (June) 1930.

2. (*a*) Greenfield, J. G.: Acute Disseminated Encephalomyelitis, in Browning, C. H., and others: System of Bacteriology in Relation to Medicine, Medical Research Council, London, His Majesty's Stationery Office, 1930, vol 3, pp. 133-139. (*b*) Milligan, R. M., and Neuburger, K.: Post-Vaccinal Encephalitis in Adults, J. Neuropath. & Exper. Neurol. **1**:416, 1942.

3. Marie, P.: Lectures on Diseases of the Spinal Cord, London, New Sydenham Society, 1895.

4. Ferraro, A.: Pathology of Demyelinating Diseases as an Allergic Reaction of the Brain, Arch. Neurol. & Psychiat. **52**:443 (Dec.) 1944.

5. Centanni, E.: Sui prodotti tossici secondarii nelle infezioni, Riforma med. **3**:637, 1898.

injected into rabbits. He reported prostration and toxemia. Hurst [6] was among the first of the present day investigators to observe paralysis in rabbits following repeated subcutaneous or intramuscular injections of saline suspensions of human brain. He found no paralysis following injections of brain of the guinea pig, sheep or monkey. Detailed histologic examination of the nervous system revealed no microscopic lesions in any of these animals. The brain tissue he injected was normal, slightly denatured by mild heat or phenolized. The next year (1933) Rivers, Sprunt and Berry [7] produced clinical neurologic disease in monkeys with repeated injections of extracts and saline suspensions of normal rabbit brain, and they also observed histologic evidence of encephalomyelitis with demyelination in the affected monkeys. Shortly thereafter Rivers and Schwentker [8] elaborated on this work and presented detailed histologic descriptions which have served as the basis of comparison for the work that has been done since. In 1940 Ferraro and Jervis [9] repeated and confirmed the work of Rivers and his co-workers. By using saline suspensions and alcohol-ether extracts of rabbit brain, they were able to produce encephalomyelitis in monkeys after repeated intramuscular injections. The monkeys received between twenty-nine and one hundred and three injections during the course of from one hundred and twelve to four hundred and five days. After a minimum of one hundred days all 7 monkeys in their series presented clinical symptoms referable to the nervous system, such as forced position of the head, tremors, nystagmus and spastic paresis. Histologically these animals, like those of Rivers and co-workers, showed many small lesions disseminated throughout the central nervous system, more particularly but not exclusively, in the white matter. Most of the lesions were perivascular and were characterized by loss of myelin and axons and by sleeves of hematogenous cells, or hematogenous and interstitial cells, in the zone immediately adjacent to the involved blood vessels. A noteworthy feature of the exudate was the presence of multinucleated giant cells, which had also been reported previously by Rivers and Schwentker.[8]

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6. Hurst, E. W.: The Effect of Injection of Normal Brain Emulsions into Rabbits, with Special Reference to the Etiology of the Paralytic Accidents of Antirabic Treatment, J. Hyg. **32**:33, 1932.

7. Rivers, T. M.; Sprunt, D. H., and Berry, G. P.: Observations on Attempts to Produce Acute Disseminated Encephalomyelitis in Monkeys, J. Exper. Med. **58**:39, 1933.

8. Rivers, T. M., and Schwentker, F. F.: Encephalomyelitis Accompanied by Myelin Destruction Experimentally Produced in Monkeys, J. Exper. Med. **61**: 689, 1935.

9. Ferraro, A., and Jervis, G. A.: Experimental Disseminated Encephalopathy in the Monkey, Arch. Neurol. & Psychiat. **43**:195 (Feb.) 1940.

The mechanism of the production of these lesions offers a fruitful field for speculation. It has been known for some time [10] that fresh, homologous brain tissue possesses little or no antigenic power. It is also well known that heterologous brain,[11] as well as homologous brain plus pig serum,[10] is capable of inciting in animals receiving them antibrain antibodies, which can be demonstrated either by the precipitin or by the complement fixation test. In 1934, in order to see whether brain haptene could be converted into a complete antigen without the addition of heterologous protein, Schwentker and Rivers [12] autolyzed sterile homologous brain tissue, which, when injected into rabbits, was definitely antigenic. In like manner, they also found that emulsions of fresh, homologous brain when infected with vaccine virus was likewise antigenic, as demonstrated by the complement fixation and the precipitin test. They further showed that embryonic and neonatal brain tissue was nonantigenic and that antigenicity increased with age and reached its maximum at maturity. Fitting in with this demonstration was the observation that the antigenicity of the white matter was about six times as great as that of the gray matter. This important investigation points to the antigenic character of the modified myelin sheath; and, because of the subsequent demyelination accompanying experimentally produced encephalomyelitis, speculation is in order as to the possibility of the involvement of a lipid antigen in such conditions as multiple sclerosis and other demyelinating diseases.

Another point may be mentioned at this time. As long ago as 1924 Lewis and Loomis [13] showed that antibody titers to substances not related to tubercle bacilli were considerably higher in tuberculous guinea pigs than they were in normal animals. Dienes and Schoenheit [14] discovered that when egg white or horse serum was injected into a tuberculous focus, such as a tuberculous gland, the sensitization to these antigens was more vigorous in that the cutaneous reactions to

10. Lewis, J. H.: Immunologic Specificity of Brain Tissue, J. Immunol. **24**: 193, 1933.

11. Witebsky, E., and Steinfeld, J.: Untersuchungen über spezifische Antigenfunktionen von Organen, Ztschr. f. Immunitätsforsch. u. Exper. Therap. **58**: 271, 1928.

12. Schwentker, F., and Rivers, T. M.: Antibody Response of Rabbits to Injections of Emulsions and Extracts of Homologous Brain, J. Exper. Med. **60**: 559, 1934.

13. Lewis, P. A., and Loomis, D.: Allergic Irritability: Influence of Chronic Infections and of Trypan Blue on Formation of Specific Antibodies, J. Exper. Med. **43**:263, 1926.

14. Dienes, L., and Schoenheit, E. W.: Local Hypersensitiveness in Tuberculous Guinea Pigs, Proc. Soc. Exper. Biol. & Med. **24**:32, 1926; Reproduction of Tuberculin Hypersensitiveness in Guinea Pigs with Various Protein Substances, Am. Rev. Tuberc. **20**:92, 1929.

these antigens appeared and disappeared more slowly and were sometimes necrotic. Dienes [15] was then able to produce the same enhanced reaction by using dead tubercle bacilli. This adjuvant technic was carried on from that point by Freund and his co-workers [16] with the use of killed tubercle bacilli, liquid petrolatum and sometimes "aquaphor" (an oxycholesterol-petrolatum ointment base), obtaining long-sustained and sometimes necrotic cutaneous reactions to antigens not related to tubercle bacilli. Using the adjuvant technic of Freund, Kopeloff and Kopeloff [17] succeeded in producing antibrain antibodies in the serum of monkeys immunized to sheep brain. Making use of the same technic while working on poliomyelitis, Morgan [18] recently produced encephalomyelitis in the monkey. Heat-killed tubercle bacilli in "falba" [18a] with homologous central nervous system tissue caused extensive encephalomyelitis in 7 out of 12 monkeys, while 8 out of 9 monkeys presented similar lesions after injections of these adjuvants mixed with spinal cord infected with virus of poliomyelitis. The adjuvants alone or with other organs produced no such disease in the central nervous system. Even more recently, Kabat, Wolf and Bezer,[19] also utilizing the adjuvant technic, but employing heterologous antigen, succeeded in hastening the reaction time in the production of encephalomyelitis in monkeys.[19a]

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15. Dienes, L.: Further Observations Concerning Sensitization of Tuberculous Guinea Pigs, J. Immunol. **15**:153, 1928. Dienes, L., and Schoenheit, E. W.: Antigenic Substances of the Tubercle Bacillus: Antigenic Substances of Synthetic Culture Medium, ibid. **18**:285, 1930.

16. Freund, J., and McDermott, K.: Sensitization to Horse Serum by Means of Adjuvants, Proc. Soc. Exper. Biol. & Med. **49**:548, 1942. Freund, J., and Bonato, M. V.: The Effect of Paraffin Oil, Lanolin-Like Substances and Killed Tubercle Bacilli on Immunization with Diphtheria Toxoid and Bact. Typhosum, J. Immunol. **48**:325, 1944.

17. Kopeloff, L. M., and Kopeloff, N.: The Production of Antibrain Antibodies in the Monkey, J. Immunol. **48**:297, 1944.

18. Morgan, I.: Allergic Encephalomyelitis in Monkeys in Response to Injection of Normal Monkey Cord, J. Bact. **51**:53, 1946.

18a. "Falba" (Pfaltz and Bauer Inc., New York), a hydrous wool fat–like adsorption base, said to be a mixture of beeswax, paraffin oils of varying viscosities and oxycholesterol extracted from hydrous wool fat.[18]

19. Kabat, E. A.; Wolf, A., and Bezer, A.: Rapid Production of Acute Disseminated Encephalomyelitis in Rhesus Monkeys by Injection of Brain Tissue with Adjuvants, Science **104**:262, 1946.

19a. Since this article was submitted for publication, new papers by Morgan and by Kabat and associates have appeared: Morgan, I. M.: Allergic Encephalomyelitis in Monkeys in Response to Injection of Normal Monkey Nervous Tissue, J. Exper. Med. **85**:131, 1947. Kabat, E. A.; Wolf, A., and Bezer, A. E.: The Rapid Production of Acute Disseminated Encephalomyelitis in Rhesus Monkeys by Injection of Heterologous and Homologous Brain Tissue with Adjuvants, ibid. **85**:117, 1947.

A further point may be noted here. It has been recently shown that the toxic filtrate (alpha toxin) of Clostridium welchii (perfringens) causes demyelination in vitro.[20] This alpha toxin contains, among other factors, a large percentage of an enzyme capable of hydrolyzing lecithin.[21] Under certain optimum conditions [20] the lecithin of the myelin sheath can be hydrolyzed, leaving the remainder of the myelin intact, thus producing a slightly abnormal myelin sheath.

It is clear from this short review that encephalomyelitis may be experimentally produced in laboratory animals by the repeated injections of heterologous brain antigen and that, as shown serologically, antibrain antibodies have been produced with the use of homologous antigen that has been changed by autolysis or made effective by the addition of adjuvants. It is likewise clear that normal adult heterologous brain tissue, especially white matter, is definitely antigenic, as shown by serologic reaction. With these ideas in mind, the present work was undertaken. It was believed that if there is any relation between the facts previously mentioned and demyelinating diseases as seen in man, the question of heterologous antigen is patently too artificial to be of universal value. The possibility of becoming inoculated with the nervous system of another species, except during the Pasteur treatment or some such special condition, is remote. But the possibility of autoantigen being derived from the patient's own nervous system has to be considered.

The purpose of the present paper is to report on the histologic nature of encephalomyelitis as it has been produced in rabbits with the use of homologous antigen.

MATERIALS AND METHODS

Antigen was prepared in five different ways. With all forms only the spinal cord was used on account of its relatively high content of white matter. In preparation of the first four types of antigen the spinal cord of the rabbit was aseptically removed, and then, after removal of most of the meninges, the cord was ground up in a mortar, care being exercised to keep the procedure as aseptic as possible. The first antigen, called "normal rabbit cord," was merely suspended in isotonic solution of sodium chloride, and a 0.3 per cent solution of phenol was added as a preservative. The second antigen, called "Welch toxin antigen," was prepared as follows: After the rabbit cord was ground up aseptically, it was thoroughly mixed with an equal volume of the toxic filtrate (alpha toxin) of Cl. welchii [22] and incubated at 37 C. for twenty-four hours. Then isotonic solution

20. Morrison, L. R., and Zamecnik, P. C.: Experimental Demyelination by Means of Enzymes, with Special Reference to the Alpha Toxin of Cl. Welchii, to be published.

21. Macfarlane, M. G., and Knight, B. C. J. D.: Biochemistry of Bacterial Toxins: I. Lecithinase Activity of Cl. Welchii Toxin, Biochem. J. **35**:884, 1941.

22. Glycerinated Cl. welchii (type A) filtrate, different batches of which have assayed as containing from 500 to 1,700 mouse subcutaneous minimal lethal doses per cubic centimeter, was obtained from Dr. Paul C. Zamecnik.

of sodium chloride was added to the mixture, and it was centrifuged for ten minutes. The supernatant fluid was decanted and fresh saline solution added. After a thorough mixing, the suspension was centrifuged again. This procedure was carried out three times, or until the supernatant fluid was clear and colorless. This suspension of residue in isotonic solution of sodium chloride was used as the antigen and was believed to contain "modified" myelin sheath. The third antigen, called "no. 3 antigen," was prepared by incubating normal rabbit spinal cord in the filtrate of Cl. welchii as in the preparation of the second antigen, but the Welch toxin was not removed. After incubation for twenty-four hours, isotonic solution of sodium chloride was added to the mixture to make a suitable dilution, and this suspension was used as the antigen. Welch toxin antigen and no. 3 antigen were phenolized in the same way as the normal rabbit cord antigen. The fourth antigen, called the "tubercle bacillus antigen," was prepared by mixing 2 cc. of ground rabbit cord with a suspension in 4 cc. of "bayol F" [22a] of tubercle bacilli killed in solution of formaldehyde U. S. P. The fifth antigen consisted of normal human spinal cord treated with solution of formaldehyde U. S. P. After removal of the cord from the meninges, small blocks were ground up in a mortar and suspended in 0.1 per cent concentration of solution of formaldehyde U. S. P. in isotonic solution of sodium chloride. The fourth antigen was used freshly prepared. The others were kept frozen on solid carbon dioxide except when in use. The first three antigens were administered intradermally on two successive days each week. One cubic centimeter of the suspension was injected in a series of eight or ten wheals on the abdominal skin, from which the hair had been plucked. When the no. 3 antigen was fresh, before the enzyme had exhausted itself on the substrate, a slight necrotizing effect was produced at each needle hole. This invariably healed in the course of a week or two. The "tubercle bacillus antigen" was given into the foot pads of the rabbit, 0.1 cc. in each foot, so that each animal received only one set of injections, totaling 0.4 cc. per animal. These injections were not repeated week after week. They were given but once. The human cord (treated with solution of formaldehyde U. S. P.) was administered intraperitoneally, three times a week, about 5 cc being given in each injection.

Animals of the first series, inoculated with normal rabbit cord antigen, were not expected to show any signs of disease of the nervous system. They were used as a partial control on animals of the second and third series, which were inoculated with modified homologous spinal cord. As a further control on the series receiving the Welch toxin antigen, glycerinated Welch toxin without the spinal cord might have been administered intradermally in semiweekly injections; such controls were not used, however, because of the severe local dermonecrosis produced, even if the animals could have survived the hemolytic effect of the enzyme. Used as a partial control, however, were mice, rabbits and dogs of another experiment which received repeated sublethal doses of Cl. welchii filtrate subcutaneously, intramuscularly and intravenously, without producing any clinical or histologic signs of encephalitis.

Either the animals were killed by the intravenous injection of air or they died. The brain and spinal cord were removed immediately after death, or early in the morning if the rabbit died during the night. Sections from different parts of the central nervous system were stained by a variety of methods after appropriate fixation. Among the most common technics used were the Nissl, hematoxylin

22a. "Bayol F" (Standard Oil Company) is liquid petrolatum, with a specific gravity of 0.825 at 60 F. and a viscosity of 50 to 55 at 100 F.

and eosin and Van Gieson stains; the Hortega method for microglia; the Cajal method for astrocytes; the Weil method for myelin sheath; oil red O for fat, and the Bodian method for axons. These stains were used routinely and were augmented by others when necessary.

EXPERIMENTS

The experiments can be divided into five groups according to the antigen used. The first four series of rabbits received injections of rabbit cord, while the fifth had injections of human cord. The animals in the first series (table 1) presented no clinical symptoms referable to the nervous system. Rabbit 10 exhibited Pasteurella infections on

TABLE 1.—*Suspension of Normal Rabbit Spinal Cord in Isotonic Solution of Sodium Chloride*

Rabbit Number	Number of Injections *	Survival Time, Days	Signs Referable to Central Nervous System	Pathologic Changes
10	95	348	—	—
13	105	392	—	—
991	104	390	—	—

* Since only about 0.1 cc. could be injected in one wheal, about ten needle holes were made in administering 1 cc. of antigen. This 1 cc. was called one injection.

TABLE 2.—*Rabbit Spinal Cord Incubated in Welch Filtrate, Toxin Removed*

Rabbit Number	Number of Injections	Survival Time, Days	Signs Referable to Central Nervous System	Pathologic Changes
29	54	195	+	+
36	55	540	—	—
42	1	8	+	+

the hindfeet, which were troublesome; so she was killed just under a year after the first inoculation.

Rabbit 42 (table 2) had but one injection, receiving 1 cc. of the antigen in eleven intradermal wheals. This antigen was freshly prepared, but after the animal was given the injection it was discovered that the preparation was not sterile; consequently, that tube of antigen was discarded. During the course of the next few days, pending the preparation of a new antigen, this rabbit manifested symptoms referable to the nervous system. The right hindleg was weak and was moved awkwardly. The rabbit slipped and fell to one side when it attempted to hop. The reflexes were increased usually, but sometimes they were difficult to elicit, especially in the right hindleg. Gradually the animal appeared more ill. Her coat was neglected; her ears drooped; she moved about less and less, ate nothing and died eight days after the inoculation. Before that time she had apparently been well.

Rabbit 29 exhibited weakness in both front paws about a week after the first inoculation. The paws flared out sideways and were drawn in awkwardly when the rabbit attempted to hop. This condition improved gradually, but the rabbit never fully recovered the complete use of the front paws. About a month after the first inoculation the animal was seized with a violent convulsion during the procedure of inoculation. This convulsion lasted about two minutes and was generalized, involving all four legs and the head and trunk. It was never repeated so far as we observed. About two months after the first injection a shaky, quivering incoordination of the hindlegs developed. This was transient and in two or three days had disappeared. The only possible sign of involvement of the nervous system that the rabbit retained was slight weakness of the front paws. It seemed unlikely that other neurologic signs would develop; so the animal was killed about six months after the first inoculation. Rabbit 36 never presented any untoward clinical signs. The injections were

TABLE 3.—*Rabbit Spinal Cord Incubated in Welch Filtrate, Toxin Retained*

Rabbit Number	Number of Injections	Survival Time, Days	Signs Referable to Central Nervous System	Pathologic Changes
16	63	238	—	+
50	12	160	—	—
104	6	19	+	+
54	12	160	—	—
308	65	347	—	+

discontinued after six months, and the animal was allowed to have a long survival time, in view of the histologic changes in rabbit 29, which had almost no clinical signs for three months before death.

Only 1 of the animals in the third series (table 3) presented clinical signs that could be definitely associated with the nervous system. Rabbit 104, after six injections, showed weakness and awkwardness of the hindlegs. The tendon reflexes were equal on the two sides, but were sluggish and not always obtainable. This weakness was progressive, and a day or two after its first appearance the rabbit dragged herself about with her forepaws, the hind extremities extending out behind. There was not complete paralysis, however, for the animal could hop in a feeble way when stimulated, after her hindlegs had been passively bent into the hopping position. The animal ate but little, became weaker, neglected her coat and died during the night, five days after the first clinical sign. Rabbit 16 also exhibited awkwardness of the right hindleg, incoordinated movements when hopping and an apparent paresis in both hindlegs. But these signs were probably caused by an abscess in the right groin, which was discovered a day or two before the animal was killed.

The animals of the fourth series (table 4) had a much prompter response. Nine out of the 10 rabbits presented clinical signs, most of them neurologic. Rabbit 435 presented no untoward signs and was alive and well five months after the inoculation. Rabbits 464 and 471 appeared sleepy, apathetic and off their diet; they neglected their coat, failed to hold their ears erect and moved about only when they were prodded. There was no apparent paresis, however. They both died suddenly, about two weeks after the injection. All the other animals of this group presented symptoms referable to the nervous system. Sometimes the front legs would be affected first, and, because of the weakness in them, the animal would fall forward on its chest, the forepaws being unable to support the weight of the body. In such circumstances the front paws would extend out laterally in a splayed fashion, and when they were moved it was in an awkward, uncoordinated

TABLE 4.—*Rabbit Spinal Cord Mixed with Killed Tubercle Bacilli in Liquid Petrolatum* [22a]

Rabbit Number	Number of Injections	Survival Time, Days	Signs Referable to Central Nervous System	Pathologic Changes
433	1 set	28	+	+
435	1 set	165	—	
441	1 set	56	+	+
458	1 set	21	+	+
463	1 set	119	+	+
464	1 set	16	—	+
466	1 set	131	+	+
471	1 set	14	—	—
472	1 set	16	+	+
487	1 set	21	+	+

manner. Usually, however, the hindpaws were most affected. Weakness, incoordination and, in a few cases, especially in the right hindleg of rabbit 463, complete paralysis were the common signs. The animal was ataxic, falling about or sliding along the side of the pen by leaning on the wall. The reflexes were usually present, even in severely paretic limbs, and response to deep pinprick was thought to be in the nature of a reflex response. In a few animals, notably rabbit 463, clonus of the hindleg could be elicited if the foot was supported by the examiner's hand while the tendons were tapped gently with the hammer. In fact, the whole body was often hyperkinetic, and, especially in the early stage of involvement of the nervous system, if the rabbit, while sitting on the floor, was unexpectedly touched with the examiner's foot, the animal would leap violently several feet forward. In a few animals clearcut neurologic signs appeared early, and later practically disappeared. This was true especially of rabbit 433. She showed great incoordination, tumbling all over herself when she hopped, falling and leaning against the wall, sometimes as though she were blind (the pupils

reacted to light), later dragging her hindquarters about by the exclusive use of the front paws. These signs gradually subsided, and for a day or two before she was killed she presented scarcely any neurologic abnormalities.

The fifth group of rabbits (table 5) is included for purposes of comparison because of the similarity of clinical signs and histologic changes. There were 5 other rabbits of this series, each of which received fewer than thirty-seven injections of the heterologous antigen treated with solution of formaldehyde, U. S. P. They all presented clinical signs referable to the central nervous system, and they all died in less than three months. The clinical signs were similar in all 6 animals and consisted in weakness of the hindlegs, incoordination, ataxia, presence of and sometimes increase in reflexes, loss of appetite, and loss of weight, followed by extreme generalized weakness, gasping for breath and, finally, death. Rabbit 398 was killed with ether while in extremis. Owing to circumstances beyond my control, the nervous

TABLE 5.—*Suspension in Saline Solution of Human Spinal Cord Treated with Dilute Solution of Formaldehyde*

Rabbit Number	Number of Injections	Survival Time, Days	Signs Referable to Central Nervous System	Pathologic Changes
398	37	92	+	+

systems of the other 5 animals of this series were not worked up histologically.

PATHOLOGIC CHANGES IN THE CENTRAL NERVOUS SYSTEM

In view of the changes observed by previous investigators, who used unmodified homologous antigen, it was not expected that any pathologic changes would appear in animals 10, 13 and 991, but, as previously mentioned, they were used as a control for the other series. Histologic examination of their brains and cords revealed nothing abnormal. There was nowhere any sign of inflammation or demyelination, and these animals had received the greatest number of injections.

The remaining groups, however, all presented histologic disease of varying degrees of intensity. The lesions were so similar in most instances that they will, in general, be described collectively, emphasis being placed on specific differences as they arise. An underlying meningoencephalomyelitis was observed in the whole series of affected animals. Sometimes the disease was almost exclusively limited to the spinal cord, sometimes to the brain, but usually lesions could be observed disseminated throughout the central nervous system. There was probably, especially in the spinal cord, a greater tendency toward involvement

of the white matter, but lesions of the gray matter were not uncommon, particularly in the brain stem and in the cerebral cortex. These parenchymatous lesions were usually perivascular foci of infiltrating and reacting cells, seen especially around small veins and, to a lesser extent, around arteries, venules, arterioles and capillaries. There was no special predilection for the periventricular regions.

The meningitis was most pronounced in the animals of the series receiving the tubercle bacillus antigen, in which it was observed in the spinal cord in all rabbits, showing pathologic changes; but it was present in a mild way in either the cord or the brain, especially on the basilar

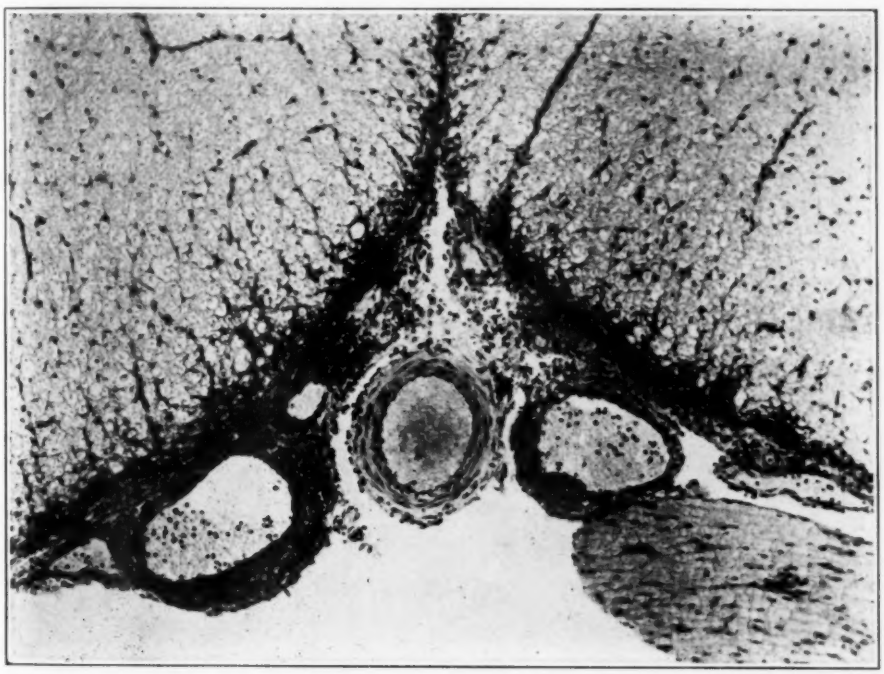

Fig. 1 (rabbit 433).—Meningitis, with the reaction involving the anterior spinal veins. The infiltration was chiefly lymphocytic, with occasional plasma cells and monocytes. Nissl stain: × 400.

surface or around the cerebellum, in most of the affected animals of whatever series. When the meningitic reaction was mild, a thin layer of lymphocytes, with occasional plasma cells, lay in the meshes of the pia-arachnoid in a patchy distribution. In rabbits with severer involvement, as in rabbit 453 (fig. 1) with early lesions, the walls of the accessory anterior spinal veins and the posterior spinal veins were densely infiltrated with eight or ten layers of lymphocytes, while in the neighboring subarachnoid space great numbers of lymphocytes and monocytes with occasional eosinophils were present. In the animals

with old lesions, such as rabbits 441, 463 and 466, the pia-arachnoid had become slightly thickened and, although the exudate had subsided, the connective tissue had proliferated. This was true, too, over the basilar surface of the brain, as well as in the spinal cord.

Beneath the pia, in the parenchyma of the rabbits receiving the tubercle bacillus antigen, whether they presented a brisk meningitis or not, there was a vigorous reaction of microglia around the edge of the cord. Indeed, in some cases a strong microglial hyperplasia was present on the periphery of the cord when no inflammation could be seen in the meninges.

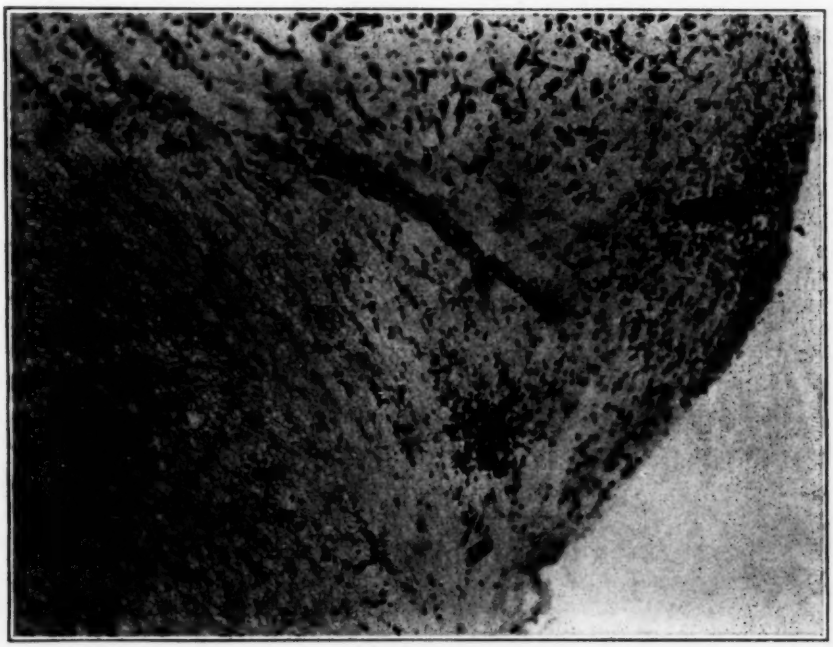

Fig. 2 (rabbit 104).—Perivascular foci of lymphocytes and microglia cells in the medulla. Nissl stain; × 100.

The inflammatory reaction followed the blood vessels as they dipped from the subarachnoid space into the substance of the spinal cord, and in the brain perivascular foci could be seen, as previously stated, in various regions remote from both meninges and ventricles. This was not an equivocal reaction but a good, vigorous response (fig. 2). Occasionally the walls of the vessel itself were infiltrated with lymphocytes; if not, the Virchow-Robin space usually contained lymphocytes, a few plasma cells and histiocytes, and even occasionally a few polymorphonuclear leukocytes. But the chief reaction was outside the Virchow-Robin space, in the parenchymatous tissue, where microglia cells in abundance were the common feature; and it is desired to emphasize

this observation (fig. 3). The microglia cells were in various degrees of activation. In some instances they had small, sausage-shaped nuclei and long spikelike processes, only slightly swollen at the base, as seen in the Hortega, or in some circumstances in the Nissl, stain. In other instances, particularly in rabbits 463 and 466, frank compound granular corpuscles were present in profusion. These cells were seen not only in the parenchyma but also as collars of fat-laden gitter cells in the perivascular space. This combination of hematogenous cells and microgliacytes was characteristic of the lesions throughout the series. Sometimes one type of cell predominated; sometimes the other. The type of cell that predominated was not determined by the case or by the

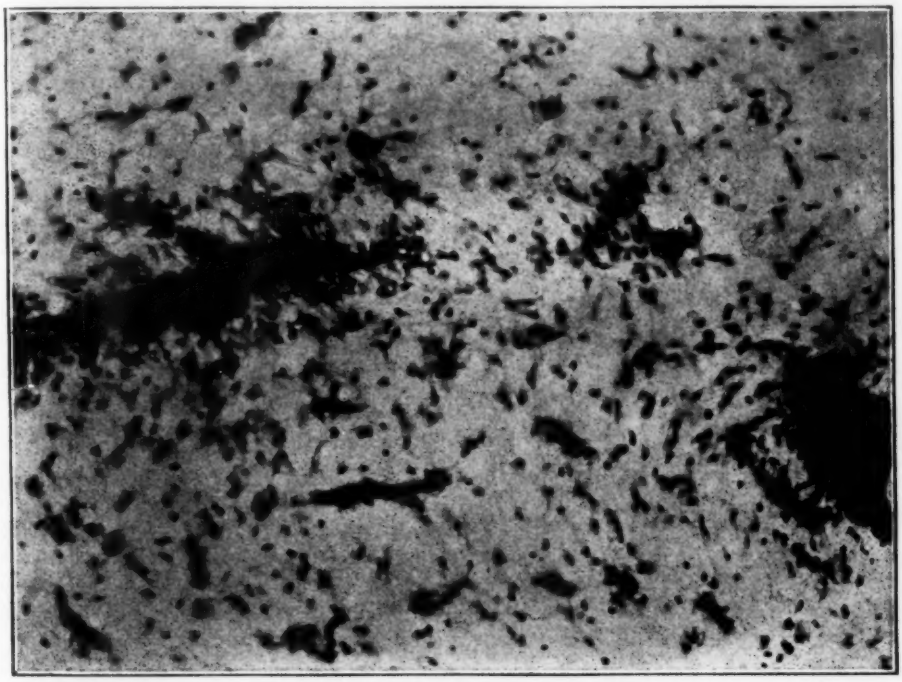

Fig. 3 (rabbit 487).—Perivascular foci of hematogenous cells and microgliacytes in the spinal cord. Nissl stain; × 100.

location. In rabbit 29, for example, in the brain could be seen occasional lesions composed practically entirely of hematogenous cells, other lesions in which only pleomorphic microglia cells were congregated around the blood vessel and still other lesions in which the microglia cells were scattered among the lymphocytes (fig. 4). In the spinal cord of animal 463, on the other hand, could be seen foci of large numbers of microglia cells in a low degree of activation; other foci presented fat-laden granular corpuscles, microglia cells in a relatively resting stage and lymphocytes.

In the immediate zone of this exudative reaction there was often destruction of myelin. This was more likely to occur when the reacting cells were microgliacytes or a combination of microgliacytes and hematogenous cells. If lymphocytes alone made up the perivascular cuffing, the loss of myelin was not noticeable, but when microglia participated in the reaction, even though the stage of activity represented by the compound granular corpuscles was not reached, there was perivascular loss of myelin, as seen in Weil's stain. This was not extensive destruction of (fig. 5) myelin; it was limited virtually to the zone occupied by the reacting cells and was usually about two or three times the diameter

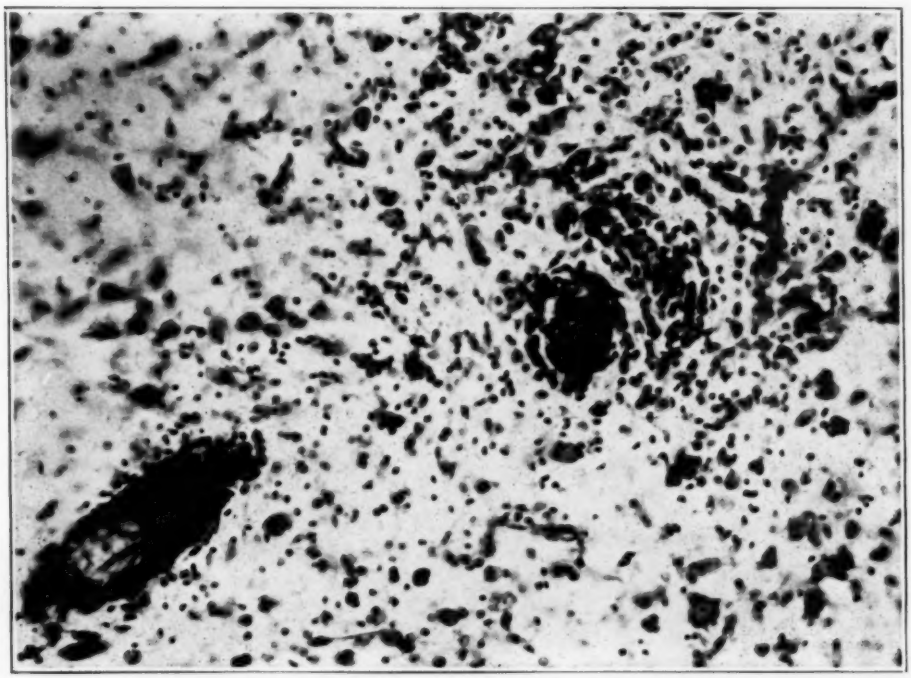

Fig. 4 (rabbit 29).—Perivascular reaction of hematogenous cells and microgliacytes. Nissl stain; × 200.

of the blood vessel it surrounded. When vessels were close together, the inflammatory process pervaded them all, and the confluent patches of demyelination were, consequently, more conspicuous (fig 8, upper part). In lesions that had existed for some time, two weeks or more, it was easy to detect fat in sections stained with oil red O. The animals receiving the tubercle bacillus antigen offer the best instances of this. In figure 6 can be seen the dense hyperplasia of microglia with the Nissl stain. These cells, with abundant, foamy cytoplasm, were practically all in the gitter cell stage. In the oil red O preparation they appeared filled with brilliant red fat. With the Hortega stain the

cells were seen to have no, or at most only the slightest vestiges of, processes. With Weil's stain this region of the cord, of course, appeared completely demyelinated.

The blood vessels presented various degrees of occlusion, which in long-standing lesions reached serious proportions, as in some of the foci observed in rabbit 29. Infiltration of the wall of the blood vessel with round cells has already been mentioned; in addition, there were many instances of hyperplasia of the intima, with swelling and piling up of the endothelium, so that the lumen was frequently considerably constricted, if not completely occluded (fig. 9). Proliferation of the subendothelial connective tissue, together with adventitial over-

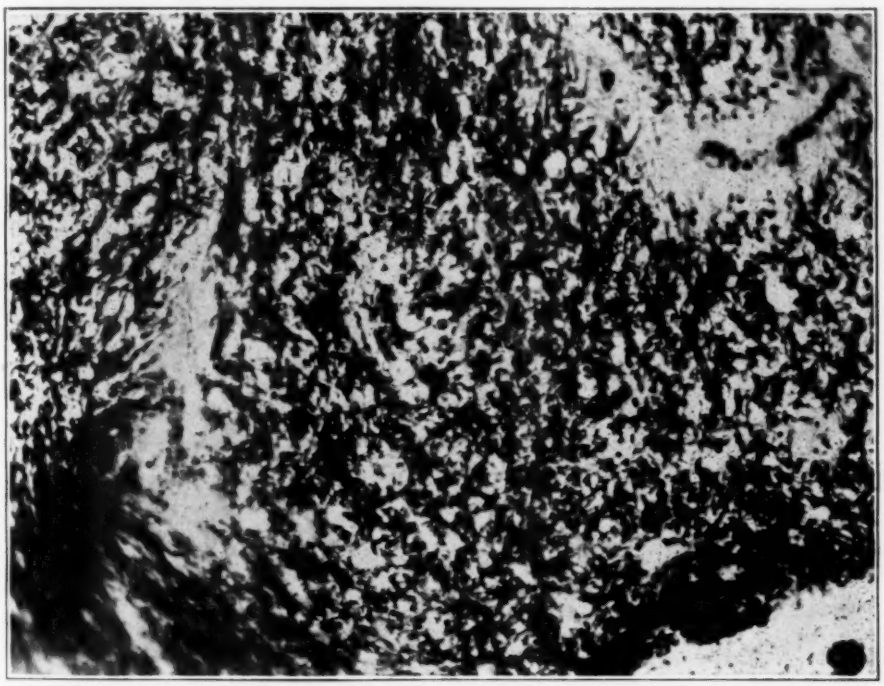

Fig. 5 (rabbit 487).—Small perivascular patches of demyelination in the spinal cord. Weil stain; × 400.

growth, gave many of these vessels thick walls. Rabbits 29 and 398 presented blood vessels with thickened walls and greatly constricted lumens more frequently than other animals.

With regard to rabbit 398, which had received the human cord antigen, it may be said that the pathologic picture was very similar to that seen in the rabbits of the other series. A few points of difference, chiefly of degree, were noted. The lesions in this case were more definitely confined to the white matter, not only in the spinal cord but also in the brain. The cerebral peduncles (fig. 10), the internal capsule,

the centrum semiovale and the corpus callosum were conspicuously spotted with dense collars of microgliacytes and round cells around the blood vessels in the perivascular spaces, and in the walls of the vessels, while the vessels so affected in the gray matter were distinctly fewer and the reaction was milder. There were, however, excellent, although fewer, lesions in the gray matter of the cervical portion of the cord and of the thalamus. Giant cells, that is, large cells with four or five nuclei, were seen occasionally in rabbit 398, not only in the meninges but also in the midst of other reacting cells in the tissue of the cord itself. These giant cells were seen occasionally, but rarely, in other rabbits, and usually only in the meningeal reaction.

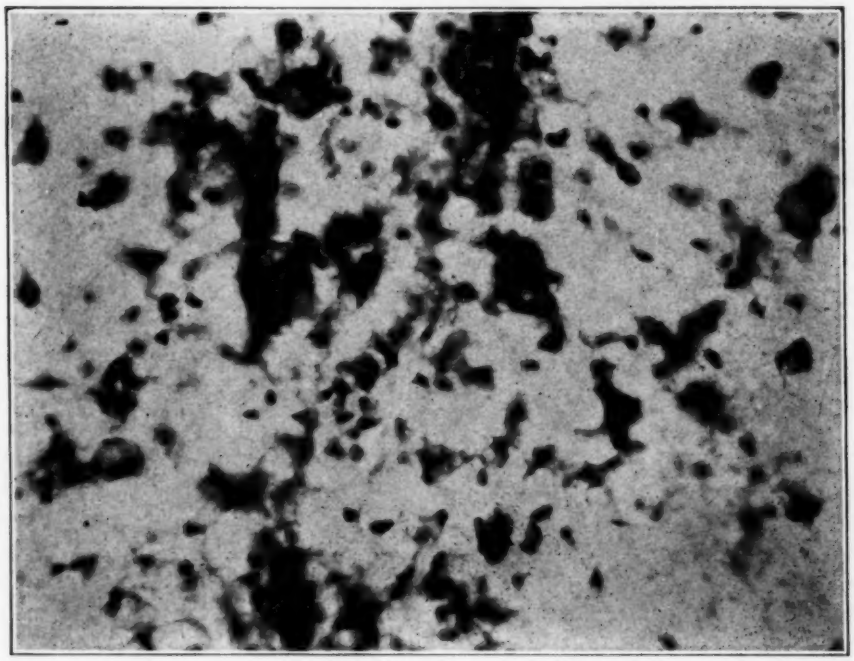

Fig. 6 (rabbit 463).—Compound granular corpuscles in the white matter of the spinal cord. Nissl stain; × 400.

A point of similarity between the pathologic picture in this rabbit and that in the rabbits in the three preceding series was that when conspicuous lesions occurred in the spinal cord the posterior column was most severely affected. The degeneration extended usually around the edge of both lateral halves of the posterior funiculus, meeting in the midline and spreading ventrally along the raphe. This degeneration consisted not only in the inflammatory reaction but in fatty degeneration, as seen with the oil red O stain, and in demyelination, as seen with Weil's stain, as well.

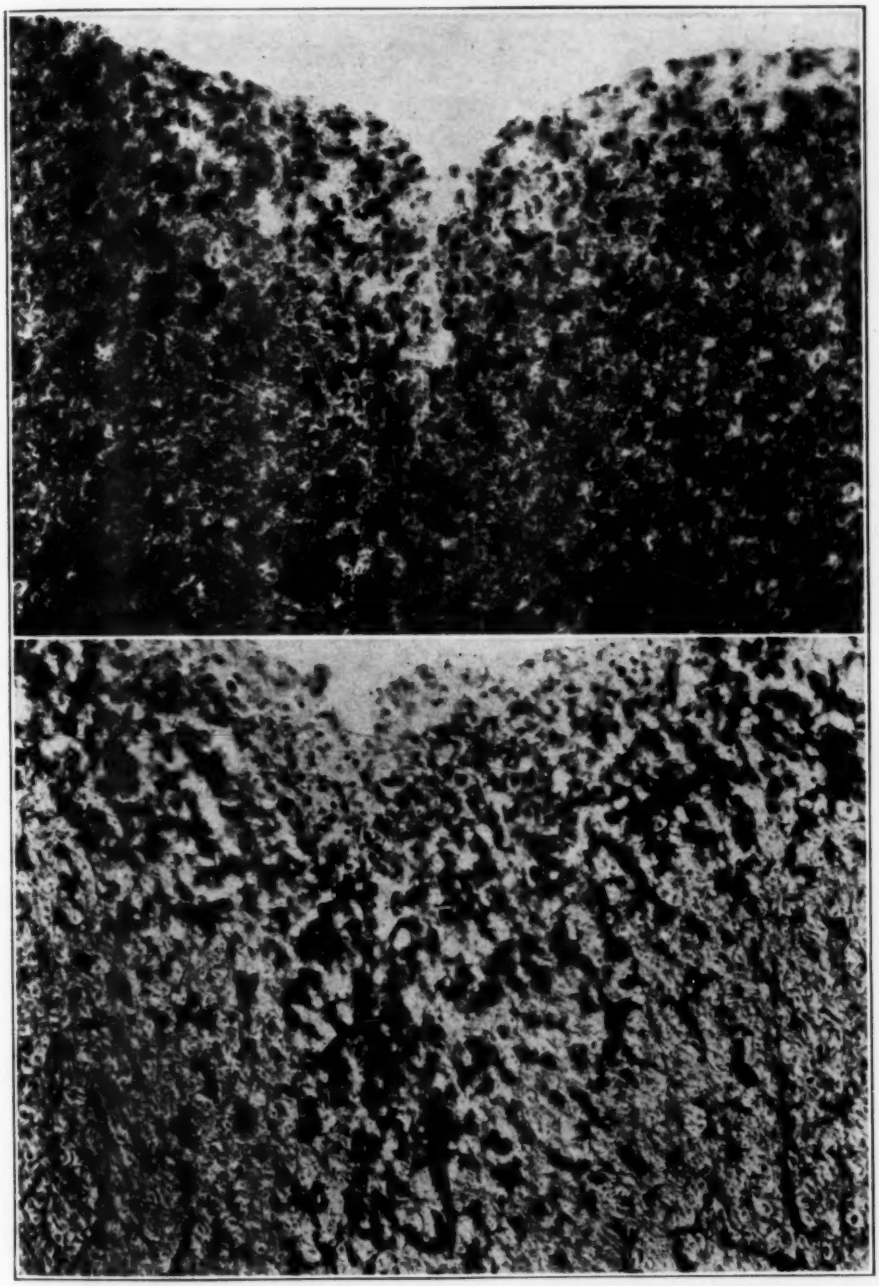

Fig. 7 (rabbit 463).—Transverse sections of the spinal cord, showing disease of the posterior columns. Upper portion, oil red O stain; × 200. Lower portion, microglia in gitter cell formation; Hortega stain; × 200.

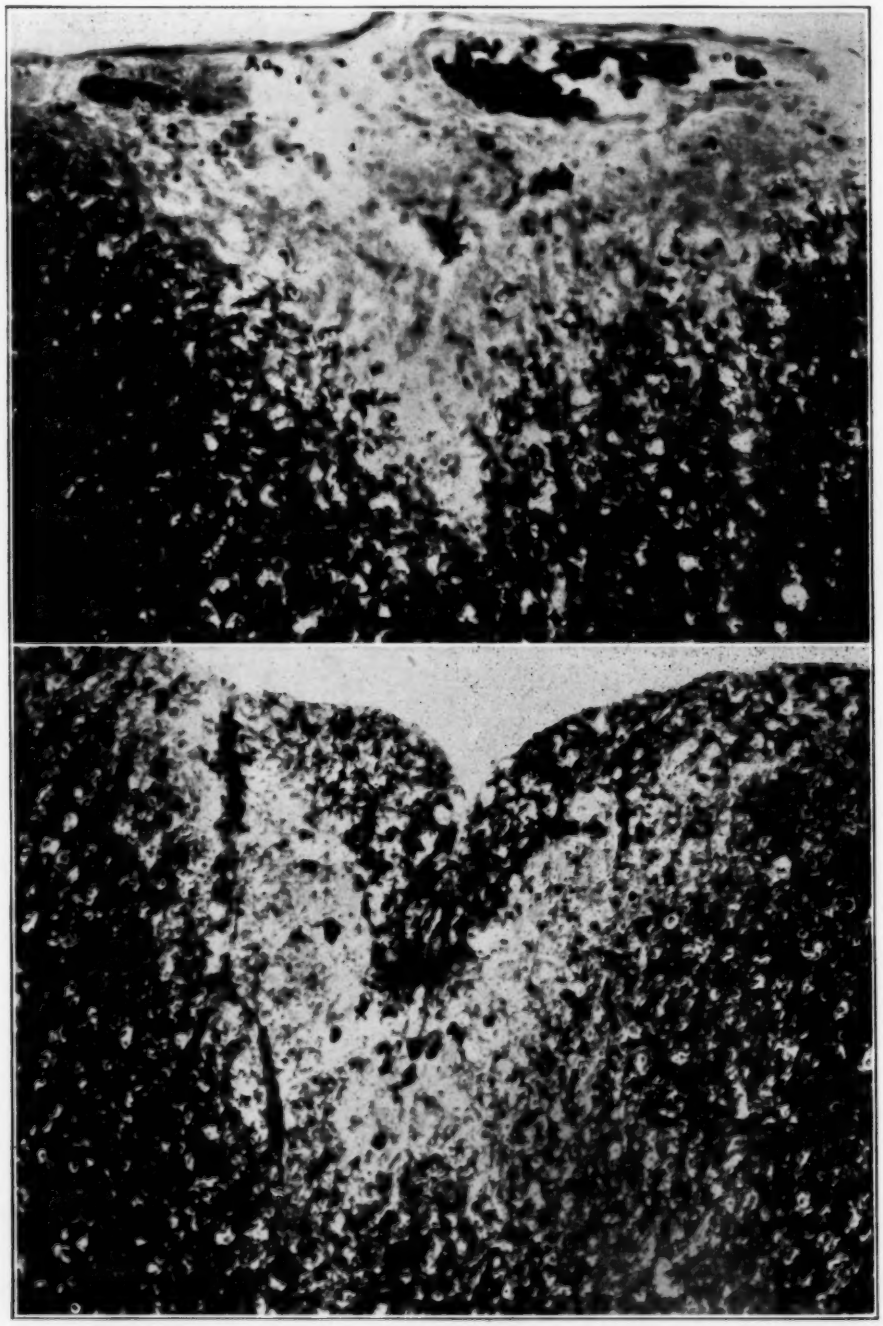

Fig. 8 (rabbit 463).—Transverse sections of the spinal cord, showing disease of the posterior columns. Upper portion, demyelination; Weil stain; × 200. Lower portion, gliosis around the periphery; Cajal gold chloride–mercury bichloride stain; × 200.

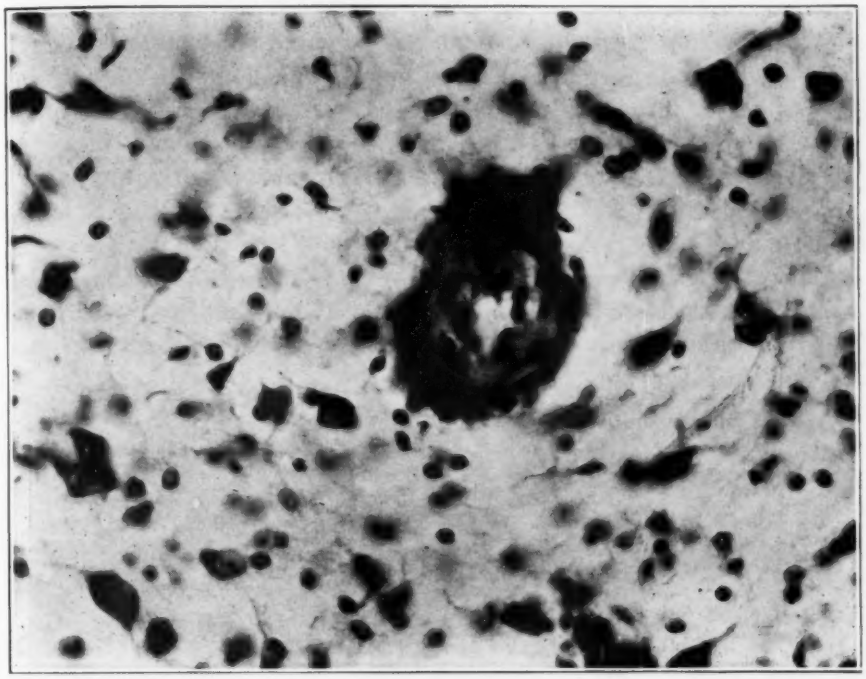

Fig. 9 (rabbit 29).—Infiltration of the adventitia, hyperplasia of the intima, swelling of the endothelium and constriction of the lumen of a small vein in the midbrain. Nissl stain; × 400.

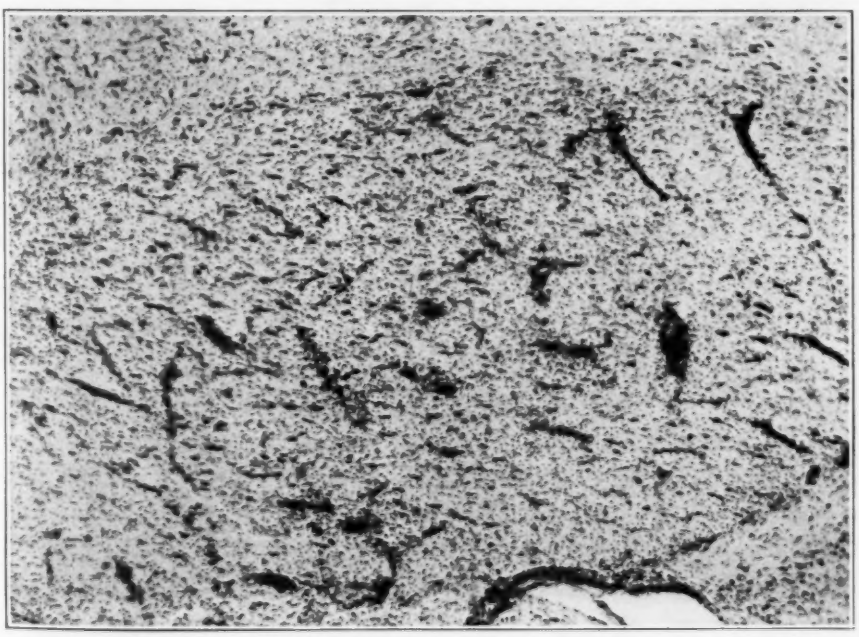

Fig. 10 (rabbit 398).—Multiple foci of perivascular cuffing of hematogenous cells and microglia cells in the peduncle. Nissl stain; × 100.

With respect to destruction of nerve cells as well as of the myelin sheaths, it may be said that disease of the nerve cell bodies was extremely rare. Retrograde degeneration, such as one might expect from involvement of the axons, was not encountered. When inflammatory foci were observed in the gray matter, the nerve cell bodies lying in the midst of the focus could be seen to be unencumbered with reacting cells. By focusing up and down through the lesion, one could clearly see normal-looking nerve cells, unattacked by microglia cells. Neuronophagia was seen on a few occasions, however. As to the axons, in the early lesions, as in rabbit 487, with a survival time of twenty-one days, they were all apparently normal. In lesions of slightly longer standing,

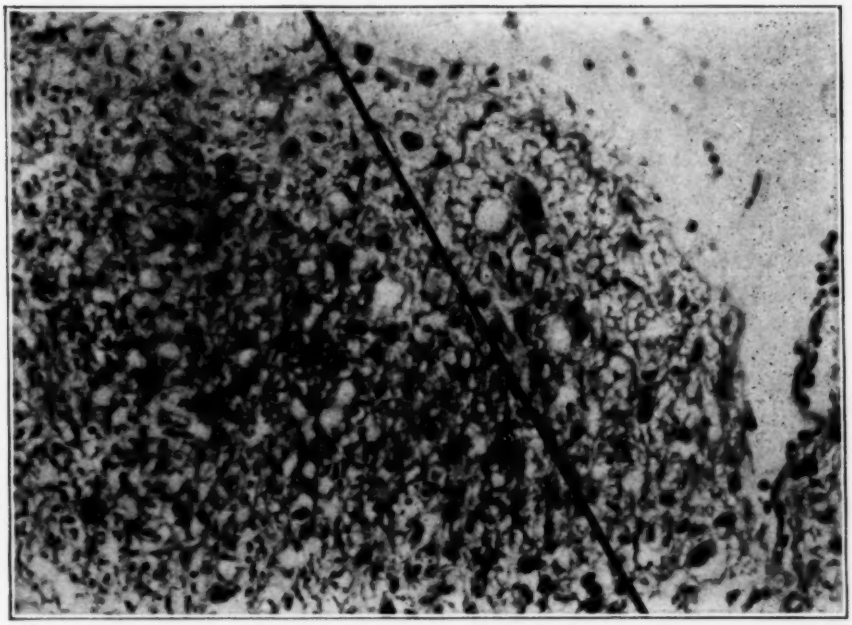

Fig. 11 (rabbit 466).—Loss of axons near the mesial and dorsal edges of the posterior column. The line divides the normal from the pathologic zone, with empty sheath spaces in the latter. Large nuclei of astrocytes are seen. Bodian stain; × 400.

such as those in rabbit 441, with a survival time of fifty-six days, some of the axons were thickened and occasional axons were missing. In older lesions, such as those in rabbit 466, which had a survival time of one hundred and thirty-one days, most of the axons in the affected zone had disappeared, leaving the sheath spaces empty (fig. 11). The greatest loss of axons was in the zone where gliosis had begun to form a fairly dense scar. In the Bodian preparations, scattered among the empty sheath spaces, and in contrast to them, could be seen the large nuclei of astrocytes. The axons in the adjoining zone—separated by

a line drawn across the photograph—appeared normal in size, number and distribution.

All the lesions in any one animal were not of the same age, and they differed in cellular makeup as a consequence. Foci containing lymphocytes and polymorphonuclear leukocytes were assumed to be the youngest lesions; yet sometimes minute perivascular foci composed entirely of microglia cells in the pleomorphic stage were encountered. Here there were no hematogenous cells at all. At any rate, various combinations of hematogenous cells and microglia cells in different degrees of activation, up through gitter cells, were present, as previously described, depending, among other things, on the age of the lesion.

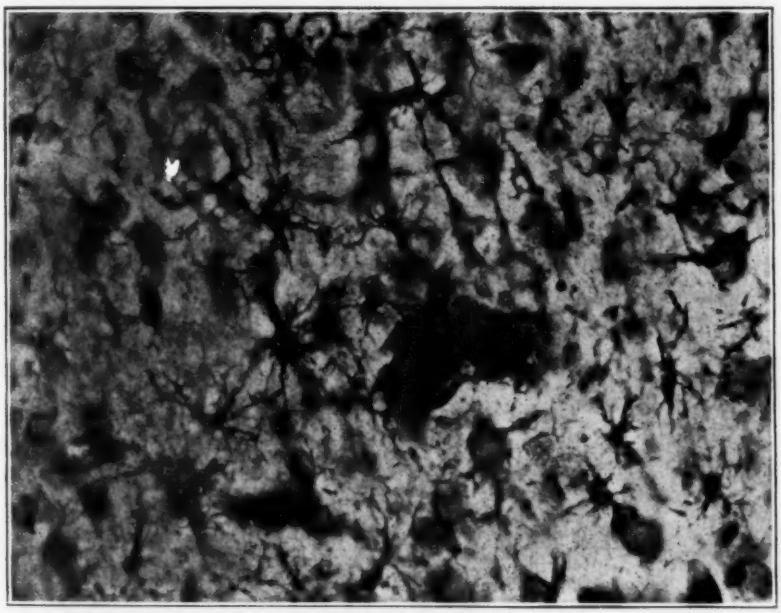

Fig. 12 (rabbit 29).—Focus of perivascular reaction of microgliacytes, showing various degrees of activation. Hortega stain; × 400.

But as these foci increased in age astrocytes participated in the reaction. Figure 8 (lower part) illustrates their response. In the spinal cord of animal 463, which had a survival time of four months, fairly dense gliosis could be seen around the edge of the cord in the Cajal gold chloride–mercury bichloride stain. The picture here was not so much a perivascular plaque as it was a deep border around the edge of the posterior column. The scar evidently arose not from the glial processes of the raphe, which was destroyed, but from astrocytes arising in the subpial zone, or growing inward from the healthy tissue beyond the demyelinated region. It will be noticed that the glial scar of figure

8 (lower part) lies in the same part of the section that was seen to be devoid of axons in figure 11.

Holzer preparations showed, in a few instances, early, delicate meshworks of beginning gliosis in the cord or brain, usually perivascular.

COMMENT

The principal histologic features of the lesions in these animals were in general similar from one series to another. Regardless of the details of the technic by which this encephalomyelitis was produced, the main characteristics were similar whether homologous or heterologous antigen was used, or whether homologous antigen was modified by enzyme-substrate activity or augmented by the action of adjuvants. In any case a perivascular reaction of hematogenous and interstitial cells was the rule, followed later by demyelination and fatty degeneration and, in chronic lesions, by astrocytic scar formation. All these characteristics can be observed in cases of multiple sclerosis,[4] although the infiltration of hematogenous cells, either in the meninges or in the parenchyma, is not a conspicuous feature of the latter disease. This is not necessarily a distinguishing difference, however, as will be mentioned later. As Ferraro [4] and Putnam [23] have repeatedly maintained, the type of lesion one sees in the various demyelinating diseases depends, to some extent at least, on the age of the pathologic process. Without belaboring this point unduly, it is suggested that there are many features of histologic similarity in the various stages of progress of multiple sclerosis, Schilder's disease, neuromyelitis optica and postinfectious and postvaccinal encephalomyelitis. Further, there is a certain similarity between these demyelinating diseases, on the one hand, and the experimentally produced encephalomyelitis reported in the present study, on the other. It is true that, except for encephalomyelitis postvaccinationem, little clue as to the underlying mechanism is available at the present time, but in the Pasteur treatment for rabies, heterologous antigen capable of inciting the production of antibrain antibodies is introduced. In the other demyelinating diseases no such starting point is known. However, Schwentker and Rivers [12] showed experimentally that homologous brain tissue, after it has been modified by autolysis, also is antigenic, as determined by the complement fixation test. Other methods besides autolysis can be used to denature or modify homologous nerve tissue so that it will become antigenic. In the study reported here it is assumed that the myelin sheath was modified by the action of the enzyme lecithinase and that this resulted in the hydrolysis of lecithin. It is not necessarily implied that hydrolyzing enzymatic activity could

23. Putnam, T. J.: Multiple Sclerosis and "Encephalomyelitis," Bull. New York Acad. Med. **19**:301, 1943.

be the underlying mechanism in the production of antigens in some of the demyelinating diseases, but it is interesting in this regard that Brickner [24] has reported a demyelinating enzyme in the plasma of patients with multiple sclerosis.

Further consideration of the pathogenesis of the lesions is based on the successful use of killed tubercle bacilli and "bayol F" as adjuvants to enhance the antibody response, in accordance with the technics of Dienes and of Freund, in bringing on clinical and histologic signs of disease of the nervous system. Results with the use of this antigen add to the conviction that the encephalomyelitic reaction is an antibrain-antibody response. The fact that the lesions are perivascular and the reacting cells are lymphocytes and microglia cells is also consistent with an immunologic response. If it is true that antibodies are synthesized in the reticuloendothelial system,[25] it is noteworthy that in the central nervous system production of antibodies and phagocytosis are carried out at the same point by the same cells, i.e., perivascularly by histiocytes. If lysis of the myelin sheath is actuated by antibodies derived from the microglia and from lymphocytes, its phagocytosis is carried on by the microglia cells. The cells predominating in these reactions were overwhelmingly microglial, and few, if any, lymphocytes were observed in the parenchymatous tissue, most of them being restricted to the walls of blood vessels, the perivascular space or the subarachnoid space. Whether the microglia was stimulated to hyperplasia by disease of the myelin in the perivascular zones, or whether it was called into activity as a source of antibodies in the zone surrounding blood vessels is, of course, not known. But it was difficult to find even the smallest lesion where microglia cells surrounded the vessel in which the myelin was not already presenting signs of the discoloration or configuration of disease. Like macrophages elsewhere, the microglia cells seemed to respond to injured tissue.

Concerning the blood-brain barrier and the passage of antibodies through it,[26] it may be said that this structure must have played some role in these experiments. The antigen, presumably, was not transported from the intradermal sites of inoculation to the brain but had existed in the brain since the earliest days, or at least since the days of maximum myelination, and had no need to cross the barrier, since it was already there. The production of brain-specific antibodies in the brain, especially in the perivascular zone, may, however, have had some functional relation to at least a part of the ectomesodermal

24. Brickner, R. M.: Studies in the Pathogenesis of Multiple Sclerosis, Arch. Neurol. & Psychiat. **23**:715 (April) 1930.

25. Dougherty, T. F.; Chase, J. H., and White, A.: The Demonstration of Antibodies in Lymphocytes, Proc. Soc. Exper. Biol. & Med. **57**:295, 1944.

26. Friedmann, U.: Blood-Brain Barrier, Physiol. Rev. **22**:125, 1942.

barrier. Since lymphocytes are now thought to transport antibodies, the confinement of these cells to the Virchow-Robin space would suggest either the passage through the pia-glia membrane of the antibodies they had been carrying or the transportation of antibodies in the parenchyma by the microglia cells. If all the antibodies were produced in situ by the microglia, it is not clear why the lesions should be perivascular or subpial. Therefore it is probable that at least some of the antibodies involved in these lesions were derived from the perivascular lymphocytes, which in some lesions were seen in abundance; and to be effective, as they were, these antibodies must have passed through, if not the blood-brain barrier, then at least the cerebrospinal fluid–brain barrier. This relation of the site of lesions to the spinal fluid has been pointed out before, especially by Greenfield,[2a] in writing of postvaccinal encephalomyelitis. It is interesting also to speculate as to whether the meningitis, with its heavy outpouring of lymphocytes, was a source of antibody production in the early days of the disease. At any rate meningitis was seen in the rabbits with the earliest lesions, such as rabbit 464, when practically no microglial reaction had yet started, and then, after reaching a peak in some of the rabbits with longer survival time, cases such as rabbit 487, it subsided, leaving only the parenchymatous lesions of perivascular and subpial microgliacytosis.

Spontaneous encephalomyelitis is a common disease in rabbits, and the possibility of its presence in laboratory rabbits must always be borne in mind. All the animals of this experiment were kept in the same room under about the same conditions. While most of them were kept in individual cages, they had opportunity to come in contact with one another twice a week on inoculation days. If spontaneous encephalitis were enzootic, it is likely that all the animals would have had lesions. Furthermore, the character of the lesions was different in the present series from that described for spontaneous encephalomyelitis.[27] While it may be argued that meningitis and perivascular cuffing with hematogenous cells of vessels of the brain could not be distinguished from lesions of spontaneous meningoencephalitis, there were other distinguishing features. Chief among these differences were the hyperplasia of the microglia and the perivascular demyelination and fatty degeneration. In more chronic lesions there was gliosis, as pointed out earlier. Another point of distinction, especially in the series given the tubercle bacillus antigen, was the severity of the lesions of the spinal cord and the appearance of clinical signs within two or three weeks of the inoculation in 9 out of 10 animals. Furthermore, although 3 animals is too small a series to have any statistical significance, the

27. McCartney, J. E.: Brain Lesions of the Domestic Rabbit, J. Exper. Med. **39**:51, 1924.

series receiving normal cord antigen, in which no lesions could be expected, remained free of lesions.

The reason that 2 of the animals showed pathologic changes without clinical symptoms is not altogether clear, but animal 104 presented only a minimal number of histologic lesions. The lesions were definite enough (fig. 2) but were not plentiful. Many sections had to be examined carefully in order to find them. Also, in the fourth series of rabbits, some animals presented extremely severe neurologic signs, which later practically disappeared; and at least 1 of these rabbits showed little activity histologically but the meninges were slightly thickened. Presumably, most of the symptoms were due to a meningitis which later subsided.

The number of histologic reaction types in the central nervous system is necessarily limited. Such factors as the reacting elements, the time sequence and the circulatory involvement can produce different pathologic pictures in different circumstances, but the types of response, while fairly characteristic, are not numerous. The reaction to virus infection is, with slight modification, the same for one virus as for another. The reaction to bacterial infection differs from the reaction to virus and differs, let us say, from the reaction to infarction. While some diseases, such as tabes dorsalis or pernicious anemia, have loss of the myelin sheath as part of their pathologic picture, they present a histologic picture in no sense to be confused with that seen in the present study. It is interesting, therefore, to point out that the type of reaction associated with multiple sclerosis, Schilder's disease and neuromyelitis optica is similar to that seen in the experimentally produced encephalomyelitis in this investigation, which is based on an immunologic reaction.

SUMMARY

Twenty-one rabbits were inoculated with rabbit spinal cord prepared in four different ways: (1) suspension of normal cord in isotonic solution of sodium chloride, (2) suspension in isotonic solution of sodium chloride of cord in which the lecithin had been hydrolyzed by lecithinase and the lecithinase then removed, (3) a similar suspension with the lecithinase left in, (4) normal cord with the addition of adjuvants "bayol F" and killed tubercle bacilli. Six other rabbits were given injections of human spinal cord treated with solution of formaldehyde U. S. P. Series 4 received but one set of injections. The four other series were given injections repeatedly for varying times, up to about a year.

Series 1 showed no clinical or histologic abnormalities. All the other series presented some cases in which there were clinical signs referable to the central nervous system and extensive histologic evidence

of encephalomyelitis. In the series treated by the adjuvant technic, 9 out of 10 animals were affected. The clinical signs were of the nature of spastic paresis, ataxia, incoordination, generalized weakness and death. The histologic lesions were usually related to blood vessels and consisted of collections of hematogenous cells in the perivascular space and in the meninges and of dense proliferations of microglia cells in the parenchyma of the spinal cord or brain. The disease showed a predilection for the white matter, where demyelination could be observed in lesions of almost any age. In animals with a long survival time early glial scars were seen.

The pathogenesis of the lesions and their possible similarity to the lesions of certain demyelinating diseases are briefly discussed.

Dr. Gardner Middlebrook, of the Rockefeller Institute for Medical Research, New York, furnished the killed tubercle bacilli in "bayol F."

Massachusetts General Hospital.

PSYCHOSURGERY DURING 1936-1946

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AND
JAMES W. WATTS, M.D.
WASHINGTON, D. C.

PSYCHOSURGERY was introduced into this country ten years ago, amid rumblings of disbelief and thunderings of disapproval. It seems appropriate now that a survey of results of the first decade be presented.

It was the experimental work of a group of investigators in Yale University that started Egas Moniz [1] on the surgical treatment of mental disorders. Jacobsen,[2] in association with Fulton, noted a profound alteration in response to frustration in the chimpanzee with both frontal poles excised. Before operation, if the animal made a few mistakes, he would scream with rage, urinate and defecate in the cage, roll in the feces, shake the bars and refuse to continue the experiments. After the operation the same animal would continue in the experimental situation long beyond the patience of the examiner, making mistake after mistake, without the least indication of being upset emotionally.

At about the same time Brickner [3] published an extensive report on the case of a man whose frontal lobes had been removed several years before because of a tumor. This man was of average intelligence, as shown by various tests following the operation, but the striking thing about him was his complete lack of self consciousness and his obliviousness to the seriousness of his own predicament. While Brickner did not mention worry by name, his patient was obviously incapable of exercising this most human of intellectual-emotional exercises.

Egas Moniz had theories of his own, but they tied in well with the findings of Fulton and Jacobsen and of Brickner; therefore he and Almeida Lima commenced operating on psychotic patients and first

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Presented at a meeting of the Connecticut State Medical Society, Sept. 10, 1946.

From the Department of Neurology, George Washington University School of Medicine.

1. Egas Moniz: Tentatives opératoires dans le traitement de certaines psychoses, Paris, Masson & Cie, 1936.

2. Jacobsen, C. F.: Studies on Cerebral Function in Primates, Comparative Psychology Monographs, Baltimore, Johns Hopkins Press, 1936, vol. 13, no. 3.

3. Brickner, R. M.: Intellectual Functions of the Frontal Lobes, New York, The Macmillan Company, 1936.

reported their results in the spring of 1936. Fulton called our attention to these reports, and by the end of 1936 we completed our first series of operations on 20 patients.[4] Seven of these patients had to have a second operation because of relapse, and 2 of them underwent three operations before the psychosis could be overcome. However, a recent check on this first series revealed that 1 patient died after operation and 5 more since, including 1 by suicide. Of the 14 living patients, 4 are employed and 4 are keeping house; 4 are living at home, and only 2 are in institutions (appendix).

At the time of our first reports[5] we emphasized the need of a long period of observation before definitive conclusions could be drawn. Up to the present time we have kept in touch with all our patients, now numbering well over 400, and the results in succeeding years are on the whole similar to those in the first series. By means of refinements in the technic of prefrontal lobotomy, we are able to secure a higher percentage of successful results in relatively favorable cases; and, knowing what could be accomplished in these, we have undertaken operation in a large number of unfavorable cases. Consequently, the percentages in the various categories of social adequacy have remained about the same over several years.

In prefrontal lobotomy the surgeon incises the white matter in both frontal lobes in such a way as to sever the connections between the thalamus and the frontal pole. From the time of our first operations we have asked ourselves what the operation does to the psychosis to make it clear up. We vividly recall the case of a young woman who was responding with intense fear to her hallucinations. They were of the most disagreeable kind, the voices calling her a dog and threatening her with hell fire. She was in a panic, and her attention could hardly be gained. Within a few hours after operation she described the same experiences but in a subdued tone of voice, as though they were hardly worth mentioning. A few days later, when questioned about the voices, she replied: "Voices? No. My ears have gone dead." This case illustrates the bleaching of the emotional tone and the quieting of anxiety that almost always accompany prefrontal lobotomy. In fact, of all the symptoms of mental disorder, emotional tension has undergone the most profound alteration after prefrontal lobotomy. This does not mean that these patients are apathetic, lacking all emotion. As a matter of fact, as they recover from the postoperative inertia, they are fairly responsive, sometimes more than they were before they became sick; but the emotion attaches itself to external

4. Watts, J. W., and Freeman, W.: Psychosurgery, J. Nerv. & Ment. Dis. **88**:589, 1938.

5. Freeman, W., and Watts, J. W.: Prefrontal Lobotomy in the Treatment of Mental Disorders, South. M. J. **30**:23, 1937.

happenings rather than to inner experiences. Patients who have been operated on are usually cheerful, responsive, affectionate and unreserved. They are outspoken, often critical of others and lacking in embarrassment. For the first few weeks or months they are rather childlike in their attitudes and behavior. They require more than the ordinary motivation to accomplish and are satisfied with something less than perfection. They tend to procrastinate, to make up their minds too quickly and to enunciate opinions without considering the various implications. Some patients are distractible, others have single track minds; some are indolent, others are human dynamos. The most striking and constant change from the preoperative personality lies in a certain unselfconsciousness, and this applies both to the patient's own body and to his total self as a social unit. The patient emerges from operation with an immature personality that is at first poorly equipped for maintaining him in a competitive society; but with the passage of time there is progressive improvement, so that in about one-half the cases earning a living again becomes possible.

On the basis of these experiences, we have advanced the hypothesis [6] that the frontal lobes are especially concerned with foresight and insight and that the emotional component associated with these functions is supplied by the thalamus. When the thalamic connections are severed, the functions of foresight and insight suffer temporary obliteration, and even in the later course of recovery are never as completely endowed with feeling tone as they were before. A modicum of function is preserved, because the direct connections are not completely severed and because indirect connections probably also exist. Foresight and insight are two very important functions for any person living in a complex society. One may well ask whether the surgeon is justified in depriving a patient of these functions even for the sake of relieving his psychosis. We believe that the surgeon would be entirely justified if it could be shown that the patient became psychotic because of perversions of these same functions of foresight and insight, together with the attachment of an abnormal emotional tone.

When one studies a psychotic patient with these functions in mind, it is not so difficult, if the case is not far advanced, to determine the fact that many of the symptoms of the psychosis may indeed be attributed to pathologic selfconsciousness. Why otherwise would a patient believe that *he* was being kept under surveillance by the F.B.I.; that German spies were entering *his* room, using thought control on *him*, putting dope

6. Freeman, W., and Watts, J. W.: Interpretation of the Functions of the Frontal Lobes Based upon Observations in Forty-Eight Cases of Prefrontal Lobotomy, Yale J. Biol. & Med. **11**:527, 1939; Psychosurgery, Springfield, Ill., Charles C Thomas, Publishers, 1942.

in *his* food or accusing *him* of sexual perversions? These ideas are intensely personal to him and preoccupy his mind to the exclusion of all rational, coherent thought processes. Or take a patient who has a string of complaints as long as his arm concerning *his* stomach and *his* bowels, *his* heart and *his* head. Here is a person, also, whose function of consciousness of the self has gone beyond normal limits into a state of hypochondriasis. His attention becomes concentrated on his various organs to the exclusion of everything else. In both cases there is also a distressing concern for the future; not only what "they" are going to do to him, but also in regard to the prospects of the ulcer, cancer or heart trouble. Above all, there is the emotional component which invests the symptoms and the ideas with a disabling force and completely prevents the patient's adaptation to the realities of existence. Such persons are sentient rather than rational beings. They live with their emotion concentrated on themselves, with an admixture of self pity or guilt that induces invalidism or, at the last extremity, suicide.

Prefrontal lobotomy cuts off the emotional component concerned with these ideas. It relieves the symptom of mental pain. In temporarily abolishing foresight and insight, the operation breaks the vicious circle of preoccupation, emotional tension and imagination that makes the suspected disease or persecution much more serious than any reality could be. It brings the patient back to earth and the enjoyments thereof.

The past decade has seen a certain vindication of our ideas on the subject of prefrontal lobotomy. Even in our first papers we cautioned against going to extremes. Now, at the beginning of the second decade, we would reiterate these cautions. Prefrontal lobotomy is an operation of last resort. It should be performed only on those patients who no longer have a reasonable hope of spontaneous recovery. It should be done only in cases of threatened disability or suicide, and only after conservative measures have failed. It should be done with the full appreciation of the changes in personality that will inevitably be brought about in the patient if the operation is to succeed, and with a knowledge of possible unfavorable results, such as persistent inertia, convulsive seizures, incontinence and aggressive misbehavior. At the same time, prefrontal lobotomy should be performed while the patient is still fighting his disease, in other words, while the emotional tension is still present to a considerable degree. When emotion subsides and the patient accepts his dream world in lieu of reality, surrenders to his fantasies, then there is little that surgery can accomplish. It has been suggested that if a patient with dementia precox fails to improve after a year prefrontal lobotomy should be considered. In view of the poor prognosis of dementia precox, we should be inclined to accept this idea. In our cases in which operation was performed within the first two years of illness the

percentage of good results was 85, whereas of those cases in which operation was done after two to thirty years of illness good results were obtained in only 31 per cent.[7]

The types of patients who respond best to prefrontal lobotomy are those with the obsession-tension states, with or without compulsions, and the chronic anxiety syndromes, with or without hysterical conversion. Twenty years of invalidism can vanish in a few weeks. Involutional depressions also clear up in a goodly percentage. Schizophrenic states are strikingly modified if the patient is excited, resistive, assaultive and disturbed. The quiet, deteriorated patients are usually unchanged. Alcoholic, psychopathic and epileptic patients, criminals and patients with organic diseases of the brain are seldom benefited.

Prefrontal lobotomy is being adopted in many parts of the world. The war interfered with the development of the procedure in continental Europe, so that the United States and Great Britain got a head start, especially so far as detailed studies are concerned. Portugal and Italy, which had been in the forefront, dropped behind. Scattered reports have come from various Latin American republics; from Sweden and Czechoslovakia; from India, New Zealand and Hawaii. More enthusiasm seems to be present in England than anywhere else. McKissock stated in April 1946 that he had personally performed 500 operations, and in the June 1946 issue of the *Proceedings of the Royal Society of Medicine* there are statistics on more than 800 cases.[8] In this country, we should estimate that up to the present time approximately 2,000 lobotomies have been performed. A recent survey by Brody and Moore[9] called attention to the rather great similarity of reports from various clinics in the percentage of patients who derive benefit from the operation. In round figures, one-third recover, one-third improve and one-third fail to improve. There are variations from one investigator to another and from one disease to another, but the results are sufficiently good to warrant the use of prefrontal lobotomy on a large scale for the relief of the very serious and chronic forms of mental disease that keep the back wards of the psychiatric hospitals filled to capacity and beyond.

We would close this review of prefrontal lobotomy by calling attention to its use in the treatment of pain due to organic disease. In case of an incurable illness, such as cancer, or of persistent pain in a phantom limb, intractable causalgia or the lightning pains of arrested tabes, the physician is likely to give up too easily and to prescribe narcotics, to

7. Watts, J. W., and Freeman, W.: Prefrontal Lobotomy: Factors Influencing the Prognosis, J. South. Med. & Surg. **108**:242, 1946.

8. Discussion on Prefrontal Leucotomy with Reference to Indications and Results, Proc. Roy. Soc. Med. **39**:443 (June) 1946.

9. Brody, E. B., and Moore, B. E.: Prefrontal Lobotomy: A Review of Recent Literature, Connecticut M. J. **10**:409, 1946.

the ultimate detriment of the patient with long-standing illness. A year ago we reported experiences in the relief of long-standing pain with prefrontal lobotomy.[10] It would seem that in cases of this condition, as in the cases of purely mental disorders, it is the emotional component, the consciousness of the part and the anticipation of the future disability and death that contribute to the distress of the patient. In many cases the attitude of the patient toward his disease is more disabling than the disease itself; the fear of pain, greater than the pain. With prefrontal lobotomy the physician now has it in his power to relieve the fear, the anticipation, and to render the illness more tolerable to the patient. Since this can be done without significant impairment of intellectual capacity, it would seem that prefrontal lobotomy might be a very considerable boon to the large number of patients whose life will not be long but will, nevertheless, be made miserable by suffering. The physician cannot be criticized for recommending prefrontal lobotomy in order to secure a certain euphoria for those patients who have only pain and death to look forward to.

APPENDIX

The 20 cases in which operation was performed in 1936 were reported in 1938.[11] A brief follow-up report as of September 1946, approximately ten years after the first lobotomy, is now given. All the patients have been kept under rather close observation at intervals of a year or less. The same case numbers are used.

CASE 1.—A housewife aged 63 had a history of agitated depression of one year's duration, with two previous nervous breakdowns. After prefrontal lobotomy she quieted down, went out socially, drove her car, kept the household accounts, enjoyed her home but took little responsibility. She had several epileptic seizures, fracturing her wrist in one of them. In 1941 she died of pneumonia. Her husband wrote that the last five years were the happiest of her life.

CASE 2.—A woman aged 59, a bookkeeper, had agitated depression of six months' duration, probably complicated by intoxication with sedatives. Prompt recovery followed prefrontal lobotomy, with return to work in three months. She continued this work for eight years, until her retirement because of age, and then returned to her office to help out during the war. She finally retired in June 1946 and has been living comfortably at home.

CASE 3.—A housewife aged 34 had obsessive preoccupation, depression and suicidal ideas of three years' duration. The first lobotomy was performed in December 1936, with little improvement; the second, in September 1937, with no change, and the third, in 1941, with extreme flattening of emotional life. She presents extreme indolence, petulance and puerility and assumes no responsibility for the care of the home. She presents a rather pleasant front but has a sterile intellectual life. She is cared for at home by her mother.

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10. Freeman, W., and Watts, J. W.: Pain of Organic Disease Relieved by Prefrontal Lobotomy, Lancet **1**:953, 1946.

11. Watts, J. W., and Freeman, W.: Psychosurgery, J. Nerv. & Ment. Dis. **88**:589 (Nov.) 1938.

CASE 4.—A housewife aged 49 had involutional depression of one year's duration (with a history of three previous attacks) and organic changes caused by a nearly successful suicidal attempt with gas. After lobotomy she continued to show apathy, loss of memory and other signs of organic disease of the brain. She had frequent convulsions and incontinence. She died in status epilepticus in 1944. Autopsy showed minimal operative lesions (all lobotomies in 1936 were done by the Egas Moniz "core" technic), but there were extensive cortical softening at the base of the frontal and temporal lobes and necrosis of the globus pallidus.

CASE 5.—A housewife aged 35 had a history of depression and agitation of four years' duration and three suicidal attempts. She benefited only temporarily from the operation, failed to make a satisfactory adjustment at home or on the farm and finally committed suicide in 1940. Autopsy was not performed.

CASE 6.—A housewife aged 60, with agitated depression, died on the sixth postoperative day of hemorrhage. Autopsy was not performed.

CASE 7.—A business man aged 59, with a history of involutional depression of nine years' duration, improved briefly after lobotomy but relapsed before he could return to his office. A second lobotomy was undertaken by a different surgeon in 1938, and the patient emerged permanently relieved of his depression but with a boisterous, arrogant and extravagant nature that required institutionalization. His condition remains unchanged, after eight years.

CASE 8.—A housewife aged 62 had a history of hypochondriasis of seventeen years' duration with superimposed agitated depression for two years. A year after operation she found part-time employment as a practical nurse and continued in this work until 1945, when she went to live with her daughter. She is fat, jolly and outspoken and is said to be "quite a worker for her age." The visceral complaints cleared up.

CASE 9.—A housewife aged 48, with involutional depression of two years' duration, had had many admissions to the hospital for abdominal complaints. No improvement followed the first lobotomy, in November 1936. The second operation was performed in March 1937, with relief. However, the patient was indolent and sarcastic and was subject to outbursts of anger, which made it necessary to confine her in an institution for eighteen months. After this she resumed her household duties, cared for her grandchildren during the war and still performs most of the domestic work in her daughter's home. On several occasions she has had fleeting depressions, only one of which was sufficiently severe to require treatment; two electroshocks were sufficient.

CASE 10.—A housewife aged 60, with agitated depression of seven years' duration, had transitory improvement after the first lobotomy, in November 1936. At the second operation, in March 1937, severe bleeding was encountered, and the operation was not completed. The patient remained unimproved and died of a heart attack the following July. Autopsy was not performed.

CASE 11.—A secretary aged 32, with catatonic schizophrenia of two months' duration and a history of a previous attack in 1934, lasting only a month, recovered rapidly, and apparently completely, after lobotomy and returned to her position. She was unable to continue because of return of emotional tension, followed by another catatonic attack, for which she was hospitalized in July 1937. Insulin and metrazol shock treatments failed to induce recovery; her family refused permission for further operation, and she remains in the hospital, greatly deteriorated, fat and inaccessible.

CASE 12.—A stenographer aged 25 entered a catatonic state in July 1936 and showed no change after unilateral prefrontal lobotomy. When operation was performed on the opposite side, she "woke on the table." She improved slowly; in a year she took a course in interior decorating but did nothing constructive with it, then returned to work as a stenographer and continued in this until 1942, when she again lapsed into a catatonic state. More extensive prefrontal lobotomy again abolished the condition, but she made a slow and imperfect recovery and was rather hostile to her family. After two years she found a clerical position and a separate domicile and continued living in this way for over a year; but when her parents became ill she returned home and has cared for them in small ways for the past year.

CASE 13.—A cement finisher aged 33 had obsessive preoccupation with his heart and general exhaustion of eighteen months' duration. After prefrontal lobotomy he was euphoric but soon relapsed. Two years later, however, he was able to resume laboring work part time. His adjustment improved with time, and for the past four years he has been steadily employed as janitor at a school, where he is highly thought of.

CASE 14.—A housewife aged 30 had agitation, feelings of unreality and probably hallucinations of six years' duration. After prefrontal lobotomy she made an erratic adjustment and was in and out of hospitals for four years. After that she was divorced, and since remarried and writes enthusiastically of her new life.

CASE 15.—A stenographer aged 42 had an acute onset of catatonic stupor in the course of rheumatic heart disease of many years' duration. Both the mental symptoms and the cardiac irregularity cleared up briefly after prefrontal lobotomy, but the improvement was not sustained. She died of congestive heart failure in April 1937 with recrudescence of mental symptoms.

CASE 16.—A housewife aged 60 had a history of obsessive-compulsive neurosis dating back thirty-six years, with intervals of good health, but with complete disability of four years' duration. Prefrontal lobotomy was followed by temporary euphoria and later return of symptoms. The second lobotomy, in March 1937, was followed by immediate disappearance of the emotional toning, but with persistence of the compulsive washing and brushing for at least three years. She presented marked increase in weight and was outspoken, tactless and disagreeable with her family. There has been steady improvement over the years, although she still shakes her skirts at imaginary dirt. She recently celebrated her seventieth birthday, and is cheerful, outspoken and rolypoly.

CASE 17.—A telephone operator aged 33, with obsessive syphilophobia of twelve years' duration, obtained partial relief from operation and was able to return to work. After a broken engagement her fears returned, and a second lobotomy was performed in 1938. She immediately lost her fears but became indolent and talkative in a silly, vapid way, was too distractible to continue at her work, helped out on a farm for a year or two and for the past two years has been steadily employed in a mill. She writes in a rather childish way of her plans for getting married.

CASE 18.—An attorney aged 37 had a history of severe psychoneurosis complicated with alcoholism of many years' duration. Prefrontal lobotomy relieved his fears but not his alcoholism, and he made an erratic adjustment for several years, enlisting in the Army and serving with the military police until his active service was terminated, after the third court-martial, with a psychiatric discharge. Since then he has been performing legal work for the Government, with inceasingly less frequent alcoholic bouts.

CASE 19.—A bookbinder aged 40 had been hypochondriacal since girlhood, with a record of twelve to eighteen abdominal operations. She had been bedridden for two years. She walked on the third postoperative day and thereafter recovered slowly, but surely. She has been employed for the past seven years at her old job. She still complains when asked about her symptoms but never mentions them otherwise.

CASE 20.—A housewife aged 40, with attacks of manic-depressive psychosis at long intervals, recovered in about a year from an episode in 1929 and was free for seven years. During the attack in 1936 she attempted suicide, sustained severe internal injuries but had only fleeting relief from depression. Prefrontal lobotomy was carried out in December 1936, with fleeting improvement. The following spring she again attempted suicide and sustained extensive burns. The clinical picture was decidedly schizoid at that time, and she was maintained in a psychiatric hospital for over a year. Finally, she received a brief course of metrazol shock therapy and recovered promptly. She has been taking care of her household satisfactorily for the past five years in spite of major domestic difficulties.

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PENICILLIN IN TREATMENT OF NEUROSYPHILIS

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THE PROPER evaluation of success in treatment of neurosyphilis has always been a problem. When Wagner-Jauregg reported the beneficial effect of malaria in treatment of dementia paralytica twenty-seven years ago, there were no objective criteria to prove his point other than clinical improvement. Since spontaneous remissions are common in dementia paralytica, most authorities insisted on an extended period of observation before accepting malaria as a therapeutic agent. A few years later it became obvious that fever therapy, unlike any previous form of treatment, at least prolonged the life span of the patient with dementia paralytica. However, it still remained uncertain whether the therapeutic success would be permanently maintained, i. e., whether the disease process had been definitely arrested. To this the clinical follow-up of the patient failed to give an adequate clue. As time went on, it was found that reversible and irreversible signs and symptoms could exist side by side in neurosyphilis and that the improvement of symptoms in some instances might be only transitory and misleading so far as the activity of the syphilitic infection was concerned. It also became increasingly evident that signs and symptoms might persist or become even more prominent although the specific process in the central nervous system had been completely checked, as proved by the fact that further antisyphilitic therapy was of no benefit. Finally, it was found that the syphilitic infection might be very active within the central nervous system and yet produce no signs or symptoms. Such activity was determined by means of changes in the spinal fluid.

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the New York University College of Medicine.

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Consequently, attention was turned to study of the changes in the spinal fluid. As early as 1924 the observation was made [1] that proper evaluation of the spinal fluid syndrome, with special emphasis on the cell count, enabled one to forecast with considerable accuracy the degree of activity of the syphilitic infection in the central nervous system. The criteria for determining activity have been given in previous papers.[2] In spite of these observations, the efficacy of treatment of neurosyphilis continues to be evaluated by some almost entirely on the basis of clinical improvement. We believe that this is a serious mistake. Little or no improvement can be expected in cases of neurosyphilis in which there has been widespread destruction of nerve tissue, as in cases of far advanced tabes dorsalis and dementia paralytica. One should never forget that antisyphilitic treatment is directed solely against the invading spirochetes and has no effect on diseased tissue except to remove the cause of the disease. Damaged nerve tissue may or may not recover function after the removal of the infection, depending on the degree and site of the damage. Because of this obvious and irrefutable fact, the spinal fluid syndrome affords the best guide to the activity of a syphilitic infection of the central nervous system and to the effect of treatment. Observations on hundreds of patients carried on over a period of years have proved the validity of this statement.[3]

A proper evaluation of the spinal fluid findings requires (1) a cell count, (2) determination of the total protein content, (3) a specific test for syphilis and (4) the colloidal gold test. The cell count affords the most valuable information as to the activity of the syphilitic infection in the central nervous system. A cell count of more than 4 per cubic millimeter is evidence of an active process. This belief is based on our own experience at Bellevue Hospital, where each year we make from 3,000 to 4,000 examinations of the spinal fluid, and on the reports of other investigators in this field.[4] An increase in total protein may

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2. (*a*) Dattner, B., and Thomas, E. W.: The Management of Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **26**:21, 1942. (*b*) Dattner, B.; Thomas, E. W., and Wexler, G.: Rapid Treatment of Neurosyphilis with Malaria and Chemotherapy, ibid. **28**:265, 1944.

3. Dattner, B.: The Management of Neurosyphilis, New York, Grune & Stratton, Inc., 1944.

4. Neel, A. V.: The Content of Cells and Protein in the Normal Cerebro-Spinal Fluid, Copenhagen, Ejnar Munksgaards Forlag, 1939. Brain, W. R.: Diseases of the Nervous System, ed. 2, London, Oxford University Press, 1940. Boyd, W. R.: The Cells in the Cerebrospinal Fluid, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932. Greenfield, J. G., and Carmichael, E. A.: The Cerebrospinal Fluid in Clinical

(Footnote continued on next page)

indicate activity of the infection, as may the colloidal gold tests. The Wassermann test determines the specificity of the process.

We have found that after successful fever therapy the first of the abnormalities of the spinal fluid to become normal is the cell count. The protein values, the readings in the colloidal gold test and the titers in quantitative Wassermann tests decrease gradually, usually in the order given. In some cases five or more years passed before the Wassermann reaction became completely negative. That the Wassermann reaction of the spinal fluid does become negative within a few years after the completion of successful treatment in many cases is proved by the records of patients treated in Wagner-Jauregg's clinic in Vienna,[3] some of whom were under observation for more than fifteen years; our own experience with malaria therapy at Bellevue Hospital, and that of other investigators.[5]

The purpose of this paper is to report our experience with penicillin in the treatment of neurosyphilis. The foregoing introduction seemed necessary, since the most objective criteria are essential in the evaluation of any therapy. We believe the spinal fluid findings, with few exceptions, afford reliable objective data in the management of neurosyphilis.

METHODS USED IN EXAMINATIONS OF THE SPINAL FLUID

Cell counts were made in the Fuchs-Rosenthal chamber, which holds 3 cu. mm. Therefore, we shall report our cell counts in thirds. The counting of 3 cu. mm. reduces the margin of error.

Quantitative protein estimations were made by a sulfosalicylic acid method, using an electrophotometer which gives reproducible readings. Values of 30 mg. per hundred cubic centimeters are regarded as the upper limit of normal.

Cell counts and total protein determinations were made both in our own laboratory and in the laboratory of the New York City Branch of the New York State Department of Health. There was excellent agreement between the findings of the two laboratories.

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5. O'Leary, P. A., and Brunsting, L. A.: The Non-Specific Treatment of Neurosyphilis, J. A. M. A. **94**:452 (Feb. 15) 1930. Plaut, F.: Klinische Verwertung der Liquoruntersuchung vom Standpunkt des Neurologen, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1929, vol. 17, p. 568. Hinsey, L. E., and Blalock, J. R.: Treatment of General Paralysis: Results in One Hundred and Ninety-Seven Cases Treated from 1923 to 1926, Am. J. Psychiat. **11**:541, 1931.

The quantitative complement fixation tests of the spinal fluid and the colloidal gold tests were made by the laboratory of the New York City Branch of the New York State Department of Health, through the courtesy of Dr. Edgar R. Maillard.

The complement fixation tests were titered in exactly the same manner as the complement fixation tests of the blood. This measurement of the reagin in the spinal fluid has proved much more satisfactory than the older method of doing complement fixation tests on varying amounts of spinal fluid.

The colloidal gold tests were made by the new Lange[6] method, which employs a sensitive gold sol made by the reduction of gold chloride with sodium citrate, a buffered solution being used as diluent. The reactions obtained with each of ten dilutions of cerebrospinal fluid are compared with a color standard ranging from 0 to 20. The numerical values are added to yield the total. This has the advantage of furnishing a quantitative as well as qualitative test. The sum of the reactions in all ten tubes in normal fluids should not be over 50. The highest possible reading in abnormal fluids would be 200. For purposes of tabulating colloidal gold curves in the tables of this report, we have chosen to give the first four figures of the older conventional colloidal gold curve when that test was used at the beginning of our survey. Since the introduction of the new Lange colloidal gold test, we report the total figure obtained by adding the numerical values in all ten tubes.

SELECTION OF PATIENTS

To eliminate variables in our experiments, we chose for treatment with penicillin only patients with "active spinal fluids," and all the patients in the series had syphilis of more than two years' duration. By the term "active spinal fluid" we mean a fluid which gives a positive reaction in the complement fixation tests for syphilis and contains more than 4 cells per cubic millimeter. The cell counts of the spinal fluids of this series of patients prior to treatment with penicillin varied from a maximum of 1,540 cells to a minimum of 16 per 3 cu. mm. In our experience we have encountered few, if any, untreated patients with active neurosyphilis who had normal cell counts of the spinal fluid.

Determinations of the total protein content of the spinal fluid of patients in this series prior to treatment varied from a maximum of 188 mg. to a low of 19 mg. per hundred cubic centimeters, only 6 patients having had below 25 mg. per hundred cubic centimeters. The highest protein values, as a rule, were found in patients with dementia paralytica.

Complement fixation titers prior to treatment varied from a maximum of 530 units to a minimum of 4 units. Only 6 patients had complement fixation titers below 10 units. There was no relation between the height of the complement fixation titer and the severity of the signs and symptoms.

First zone colloidal gold curves were reported for practically all the patients with dementia paralytica, the highest total reading having been 190. First zone colloidal gold curves with high total readings were also found for many patients with diseases diagnosed as asymptomatic neurosyphilis, meningovascular syphilis and tabes dorsalis.

EVALUATION OF PENICILLIN IN TREATMENT OF NEUROSYPHILIS

Examinations of the spinal fluid were made immediately before treatment with penicillin and at three month intervals thereafter for the first twelve to eighteen

6. Lange, C.: Methods for the Examination of Spinal Fluid, Am. J. Syph., Gonor. & Ven. Dis. **23**:638, 1939.

months and then every six months. In addition, patients were checked every month with titered complement fixation tests of the blood. While we deliberately relied primarily on the laboratory data as our guide to treatment, clinical manifestations were by no means ignored. Every patient was thoroughly examined before treatment and at regular intervals thereafter. We are well aware that from the point of view of public health, as well as that of the patient, the final goal in therapy is normal function or the regaining of as much function as possible. The desire to renew proper function, however, cannot serve as the primary factor in a scientific evaluation of the effect of treatment in arresting or eliminating an infection.

Further to reduce the variables, we used penicillin exclusively and administered it to all patients intramuscularly in individual doses dissolved in water at three hour intervals. The only variants were the number of injections and the amount of penicillin given in different groups. The total dose varied from 2,000,000 to 9,000,000 Oxford units, only 1 patient having received 9,000,000 units. The number of injections varied from seventy-five to two hundred. No patient received intrathecal therapy, and no additional treatment with other drugs was given during or after administration of penicillin.

Because of the shortage of penicillin early in the course of the study, we originally treated numerous patients having no or mild symptoms with as little as 2,000,000 units. For the past ten months we have adopted a schedule calling for individual injections of 40,000 units of penicillin every three hours for one hundred and fifty doses, making a total of 6,000,000 units for all patients with "active spinal fluids," regardless of the symptoms and signs. In our experience, it is not true that patients with late asymptomatic neurosyphilis require less treatment than patients with other forms of neurosyphilis.

One hundred and fifty-one patients treated with penicillin were followed with clinical examinations and studies of the spinal fluid for six months or more after treatment. The longest period of observation was twenty-eight months. We chose six months as the minimum period of observation because with malaria therapy we found that less than 2 per cent of the patients with normal cell counts of the spinal fluid six months after treatment relapsed at a later period. The percentage of relapses after six months of follow-up observation among patients treated with the smaller amounts of penicillin was slightly higher than that after malaria therapy. Consequently, in reporting on patients observed for only six months after treatment, we recognize the possibility that some of them may relapse at a later period.

In tabulating statistics, we included among patients considered to show a satisfactory response all those who had normal cell counts of the spinal fluid and satisfactory improvement in other spinal fluid findings, i.e., definite decreases in titer in complement fixation tests and in the total protein values, as well as improvement in the colloidal gold curves. All but 8 of the patients included in the group showing satisfactory response to treatment had transitional abnormalities in the spinal fluid in that the reactions to the complement fixation tests and the colloidal gold tests were still abnormal. The spinal fluids of the 8 exceptional patients became completely normal between nine and twenty-four months after treatment. For some of the patients with transitional abnormalities of the spinal fluid the total protein is not entirely normal at the time of writing.

Among the patients representing therapeutic failures after the original course of penicillin therapy were included all those who did not have a normal cell count of the spinal fluid six months after therapy or who relapsed at some later period. All but 3 were again treated. These 3 patients have been notified to return to the hospital for retreatment.

Table 1 gives the status of 151 patients on the basis of their original treatment. Table 2 shows the management and disposition of the 20 patients who did not respond satisfactorily to the original treatment. Table 3 gives the present status of 151 patients, including the results of treatment.

TABLE 1.—*Results of First Course of Treatment in One Hundred and Fifty-One Cases of Neurosyphilis*

Type of Neurosyphilis	Total Number of Patients	Satisfactory Response	Failure	Patients Retreated After Therapeutic Failure
Asymptomatic	23	17	6	5
Meningovascular	35	28	7	5
Tabes dorsalis	41	37	4	4
Dementia paralytica	33	30	3	3
Tabetic form of dementia paralytica	19	19	0	0
Total	151	131 (67%)	20 (13%)	17

TABLE 2.—*Analysis of Unsatisfactory Results After First Course of Penicillin Treatment*

Case No.	Type of Neurosyphilis	Original Dose, Million Units	Retreatment Dose, Million Units	Present Status
1	Asymptomatic	2	8	Satisfactory *
2	Asymptomatic	2	8	Satisfactory *
3	Asymptomatic	2	6	Indefinite †
4	Asymptomatic	3	8	Indefinite †
5	Asymptomatic	2	6	Indefinite †
6	Asymptomatic	2	None	Failure ‡
7	Meningovascular	3	8	Satisfactory *
8	Meningovascular	4	8	Indefinite †
9	Meningovascular	3	8	Indefinite †
10	Meningovascular	4	8	Indefinite †
11	Meningovascular	2	8	Indefinite †
12	Meningovascular	6	None	Failure ‡
13	Meningovascular	2	None	Failure ‡
14	Tabes dorsalis	4	5	Failure (patient died) ‡
15	Tabes dorsalis	2	6	Indefinite †
16	Tabes dorsalis	2	8	Indefinite †
17	Tabes dorsalis	4.5	8	Indefinite †
18	Dementia paralytica	5	8	Satisfactory *
19	Dementia paralytica	5	8	Indefinite †
20	Dementia paralytica	6	8	Indefinite †

* Patient followed for six or more months after retreatment.
† Present status indefinite because of inadequate follow-up period after retreatment or because of a borderline spinal fluid syndrome.
‡ Patient needs retreatment.

The patients who were retreated and whose spinal fluid findings are now satisfactory are included with the patients whose response is considered satisfactory: Seventeen were retreated. Four of these are listed in the group showing a satisfactory response, for a follow-up period of six months or more shows a satisfactory transitional spinal fluid spectrum. A greatly debilitated patient with tabes dorsalis died, although he had received two courses of penicillin, three months apart.

of 4,000,000 and 5,000,000 units, respectively. The 12 other patients were listed in the group with an indefinite status because the period of observation had not yet been sufficient or because the spinal fluid syndrome was borderline. For none of these 12 patients, however, can the result be classified as a failure at the time of this report. Of the 20 patients whose responses were considered unsatisfactory after the first course of treatment, 12 originally received only 2,000,000 or 3,000,000 units of penicillin, an amount which we now regard as inadequate.

TABLE 3.—*Present Status of One Hundred and Fifty-One Patients Treated for Neurosyphilis, Including Those Retreated*

Diagnosis	Total No. of Patients	Satisfactory	Indefinite	Failure
Asymptomatic neurosyphilis	23	19	3	1
Meningovascular syphilis	35	29	4	2
Tabes dorsalis	41	37	3	1
Dementia paralytica	33	31	2	0
Tabetic form of dementia paralytica	19	19	0	0
Total	151	135 (90%)	12 (7%)	4 (3%)

TABLE 4.—*Dose of Penicillin in First Course of Treatment of Neurosyphilis*

Diagnosis	Total No. of Patients	Dose, Millions of Oxford Units					
		2	3	4	5	6	9
Asymptomatic neurosyphilis	23	15	1	6	0	1	0
Meningovascular syphilis	35	5	8	13	0	9	0
Tabes dorsalis	41	4	21	9	1	6	0
Dementia paralytica	33	0	0	23	5	4	1
Tabetic form of dementia paralytica	19	0	1	15	0	3	0
Total	151	24	31	66	6	23	1

In addition to the patients whose response to the first course of penicillin was regarded as an unquestionable failure 6 patients with normal cell counts six months after the original course of penicillin therapy were treated again because of our desire to see whether further clinical improvement could be achieved with additional penicillin therapy. The results of treatment of these patients did not convince us that additional treatment with penicillin resulted in further improvement of function.

Table 4 gives the dose of penicillin originally given to patients classified according to the involvement of the central nervous system.

Table 5 gives the length of follow-up observations on 135 patients classified as giving a satisfactory response to treatment. Of this group, 100 were observed from twelve to twenty-eight months. Most of them still have transitional abnormal spinal fluid findings, but we believe that

in the course of time they will have completely normal fluids, as indicated by the continuous and persistent trend toward normality in all the spinal fluid findings. From past experience with fever therapy, we have good reason to believe that further treatment with either peni-

TABLE 5.—*Period of Observations of Follow-Up on Patients with Satisfactory Response to Treatment for Neurosyphilis*

Diagnosis	Total No. of Patients	Period, Months				
		6	9	12	18	24 or More
Asymptomatic neurosyphilis	19	1	0	9	8	1
Meningovascular syphilis	29	6	8	8	2	5
Tabes dorsalis	37	6	4	8	11	8
Dementia paralytica	31	5	1	13	5	7
Tabetic form of dementia paralytica	19	2	2	4	7	4
Total	135	20	15	42	33	25

TABLE 6.—*Success of Treatment of Patient* with Tabetic Form of Dementia Paralytica with Penicillin After Failure of Malaria Therapy*

Test Number	Date	Wassermann Reactions		Spinal Fluid Findings			
		Blood	Spinal Fluid	Colloidal Gold Curve	Total Protein, Mg./100 Cc.	Pandy Reaction 3	Cell Count, Cu. Mm.
1	2/13/42	4+	4+	55555†	60	4+	225
February 1942—Tertian Malaria (8 paroxysms) and 10 Daily Injections of "Mapharsen" ‡ (0.06 Gm.)							
2	9/ 7/42	4+	4+	3344†	35	3+	21
October 1942—Quartan Malaria (9 paroxysms) and 10 Daily Injections of "Mapharsen" ‡ (0.06 Gm.)							
3	2/ 4/43	4+	4+	0111†	33	3+	44
January-June 1943—20 Injections of "Melarsen" §							
4	6/28/43	4+	4+	2211†	35	3+	5
June 1943-January 1944—20 Injections of "Melarsen"							
5	5/29/44	4+	4+	0111†	48	Faint trace	18
6	10/ 2/44	4+	4+	1111†	71	4+	160
October 1944—4,000,000 Units Penicillin							
7	10/30/44	12‖	37‖	84¶	56	3+	54
8	12/ 4/44	12	30	82	45	2+	1
9	2/ 5/45	9	21	70	43	Faint trace	8
10	5/22/45	6	20	72	44	Faint trace	4
11	8/ 6/45	3	12	43	34	Faint trace	3
12	1/21/46	4	13	44	31	Faint trace	3
13	5/13/46	2	6	48	31	Faint trace	1

* A white man aged 38.
† Readings were made of the first four tubes with the older Lange colloidal gold test.
‡ "Mapharsen" is oxophenarsine hydrochloride.
§ "Melarsen" is a pentavalent arsenical (sesquisodium salt of N-[*p*-arsonophenyl]-melamine).
‖ Titered in units.
¶ The figure represents the sum of readings in all ten tubes with the new Lange method.

cillin or fever will not improve the clinical picture for these patients with transitional abnormal spinal fluid findings.

Among the patients giving satisfactory responses were 3 with dementia paralytica whom we had previously given malaria treatment and large

amounts of chemotherapy, including trivalent and pentavalent arsenical drugs and bismuth preparations, without reducing the cell count of the spinal fluid to normal. Their spinal fluid findings improved satisfactorily after penicillin therapy, and all have now been under observation for more than a year after penicillin was given. Table 6 gives the spinal fluid findings for 1 of these patients before and after treatment with penicillin.

Table 7 contains data on a patient who relapsed after treatment with only 2,000,000 units of penicillin but who responded satisfactorily after retreatment with 8,000,000 units.

The fact that 17 patients were retreated is a reflection less on the effectiveness of penicillin than on the adequacy of the dose. Even with

TABLE 7.—*Response to Retreatment of Patient* with Asymptomatic Neurosyphilis After Failure with 2,000,000 Units of Penicillin*

Test Number	Date	Wassermann Reaction: Blood	Wassermann Reaction: Spinal Fluid	Spinal Fluid Findings: Colloidal Gold Curve	Spinal Fluid Findings: Total Protein, Mg./100 Cc.	Spinal Fluid Findings: Pandy Reaction	Spinal Fluid Findings: Cell Count, Cu. Mm.
1.....	4/17/44	4+	4+	4444†	25	+	100
2.....	5/16/44	4+	4+	3321‡	25	Faint trace	98
	May 1944—2,000,000 Units Penicillin						
3.....	5/29/44	100	4+	1221†	21	0	15
4.....	7/31/44	84	4+	1110†	12	0	2
5.....	11/21/44	66	9§	50‡	18	0	7
6.....	5/22/45	62	27	107	27	0	70
7.....	6/ 4/45	62	41	122	25	Faint trace	332
	June 1945—Retreatment with 8,000,000 Units Penicillin						
8.....	7/ 9/45	53	27	102	24	+	41
9.....	9/11/45	67	19	97	14	0	2
10.....	12/17/45	44	15	58	16	0	1
11.....	3/11/46	41	12	53	13	0	3
12.....	7/ 2/46	27	10	45	16	0	2

* A Negro woman aged 26. The patient had previously been treated with thirty injections of neoarsphenamine and thirty-four injections of "mapharsen" (oxophenarsine hydrochloride).
† Readings were made of first four tubes by the older Lange colloidal gold test.
‡ The figure given represents the sum of readings in all ten tubes with the new Lange method.
§ Titered in units.

the low dose of penicillin used in many cases, slightly better results were achieved with penicillin than we found after malaria treatment and intensive arsenotherapy.[2b]

Thus, in our experience penicillin has proved to be a surprisingly effective therapeutic weapon in cases of neurosyphilis. Not only has it proved to be as effective as malaria, in our experience, but it also has the great advantage of being much less dangerous to the patient. Clinical improvement in all groups, including the patients with dementia paralytica, has compared favorably with that following malaria therapy, and we believe that penicillin will ultimately replace fever therapy.

SUMMARY

Criteria for evaluation of therapeutic success in neurosyphilis are discussed.

One hundred and fifty-one patients with active neurosyphilis were treated exclusively with intramuscular injections of penicillin every three hours, the dose and the length of therapy being varied.

One hundred and thirty-five patients (90 per cent) responded satisfactorily; 100 of these were followed for twelve months or more. The longest period of observation was twenty-eight months.

The optimum dose of penicillin is yet to be established, but our experience has led us to adopt a schedule of 40,000 units injected intramuscularly every three hours for one hundred and fifty doses, a total of 6,000,000 units.

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THE ELECTROENCEPHALOGRAM IN PORENCEPHALY

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PORENCEPHALY has been defined as a defect in cerebral or cerebellar structure appearing as a cystlike cavity communicating with the ventricles or separated from them only by a thin layer of brain tissue, covered on the outside by the pia-arachnoid and filled with a clear, colorless fluid.[1] The etiologic factors in this condition, which is usually initiated during the developmental period, may be various—inflammatory process, embolism or thrombosis, internal hydrocephalus or trauma.[2] Most probably, whatever the fundamental cause, the porencephalic cyst results from ischemic necrosis of the brain tissue and resorption of the products of liquefaction.[3]

A history of birth injury, failure of growth and paresis of one side of the body, and of convulsive seizures, together with physical findings of spastic hemiparesis, with sensory (particularly topognostic) defect and hypoplasia, is common in cases of porencephaly, since most often this defect of the brain lies in the central region.[4] Not uncommonly, homonymous hemianopsia is also present and with porencephaly of the occipital lobe may be the only physical finding of significance. Pneumoencephalographic evidence of an air-filled cyst communicating with a ventricle is diagnostic.

De Sanctis, Green and Larkin,[5] in their study of 3 cases, found the electroencephalogram to be of limited value in confirmation of the

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From the Department of Neurology and Neurological Surgery, University of Illinois College of Medicine and the Illinois Neuropsychiatric Institute.

1. LeCount, E. R., and Semarak, C. B.: Porencephaly, Arch. Neurol. & Psychiat. **14**:365-383 (Sept.) 1925.

2. Yakovlev, P. I., and Wadsworth, R. C.: Double Symmetrical Porencephalies (Schizencephalies), Tr. Am. Neurol. A. **67**:24-29, 1941.

3. Kundrat, H.: Die Porencephalie: Eine anatomische Studie, Graz, Leuschner & Lubenski, 1882.

4. Siegmund, H.: Die Entstehung von Porencephalien und Sklerose aus Geburtstraumatischen Hirnschädigungen, Virchows Arch. f. path. Anat. **241**:237, 1923

5. De Sanctis, A. G.; Green, M., and Larkin, V. DeP.: Porencephaly, J. Pediat. **22**:673-689, 1943.

diagnosis of porenchephaly and in localization, electrical tracings giving some indication of the part of the brain involved and occasionally revealing the tendency to convulsions. Pseudoporencephaly (cerebral cyst not communicating with the ventricular system or the result of trauma or abscess formation after the developmental period) has been reported to indicate its presence electroencephalographically in terms of slow waves and spikes.[6]

Nine cases of porencephaly, either true or the result of trauma or abscess, are the subject of this presentation. In all, the diagnosis was established by pneumoencephalography. In all but 1 case the electroencephalogram was abnormal. A definite difference in the amplitude of electrical potentials from homologous areas in the two hemispheres was a consistent finding in the cases of true porencephaly. Slow waves, usually constituting a focus restricted to the lobe of the brain involved, with or without spike seizure discharges, were found in the cases of post-traumatic or postinflammatory cyst when abnormalities were present.

REPORT OF CASES

TRUE PORENCEPHALY

CASE 1.—L. C., a 17 year old white girl, was admitted to the Illinois Neuropsychiatric Institute on July 8, 1942 because of right-sided convulsions of ten years' duration. The family history was without significance save for hereditary left handedness, which the patient also exhibited. An obstetric complication had necessitated the use of forceps at the patient's birth. Difficulty in using the right hand and weakness of the right arm were noted early in infancy. Right-sided jacksonian seizures had occurred at intervals during the previous ten years, and five weeks before admission the patient had a succession of such seizures amounting to status epilepticus.

Physical examination disclosed two palpable grooves (probably forceps marks) along the frontotemporal suture line. The right arm was congenitally atrophic, and the measurements of the right leg were less than those of the left. There was a supranuclear paresis of the right side of the face, and the right extremities were spastic. Reflexes were increased on this side, and the Babinski and Hoffmann signs were elicited. Examinations of the blood, urine and spinal fluid gave results within normal limits. The serologic reactions were negative.

The electroencephalographic record was characterized by generalized 4 to 7 per second activity with prominent asymmetry of amplitude (fig. 1 *A*), the height of the potential being lower over the entire left hemisphere. There was also generalized, irregular slowing.

The pneumoencephalogram revealed a huge porencephalic cyst in the left occipital region communicating with the ventricle (fig. 2). The wall of the cyst appeared thin, and there was no subarachnoid air overlying it. The ventricular system was shifted to the side of the porencephaly.

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6. Goldensohn, L. N.; Marmor, J., and Meyer, B. C.: Pneumo-Encephalographic and Electro-Encephalographic Localization of an Epileptogenic Focus, J. A. M. A. **114**:1345-1346 (April 6) 1940.

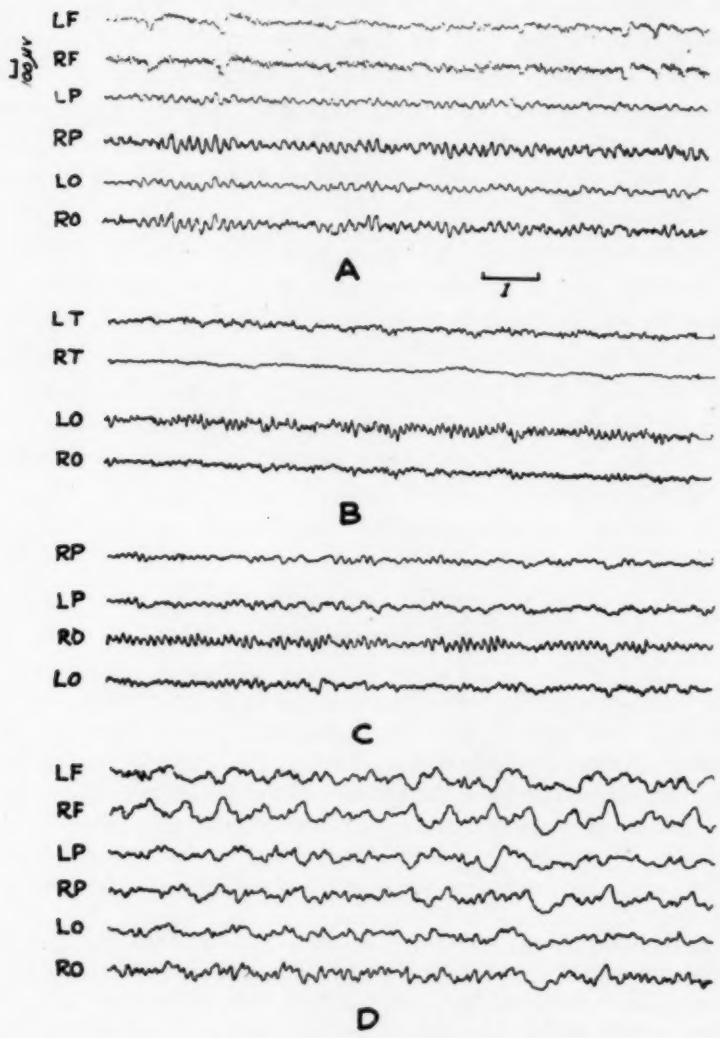

Fig. 1.—Electroencephalograms in cases of true porencephaly. *F* indicates frontal; *P*, parietal; *T*, temporal; *O*, occipital; *R*, right, and *L*, left.

A (case 1), asymmetry of amplitude, especially evident in recordings from the parietal area, with potentials of lower amplitude in the left hemisphere, associated with porencephaly in the left occipital region.

B (case 2), asymmetry of amplitude, most striking in the temporal leads, with potentials of lower amplitude in the right hemisphere, associated with porencephaly in the right occipitotemporal region.

C (case 3), asymmetry of amplitude, notable in recordings from the occipital potentials of lower regions, with lower amplitude on the left side, associated with porencephaly of the left frontocentral region.

D (case 4), asymmetry of amplitude with lower amplitude in the left hemisphere, with many slow waves from the right hemisphere, associated with porencephaly of the left frontoparietal region.

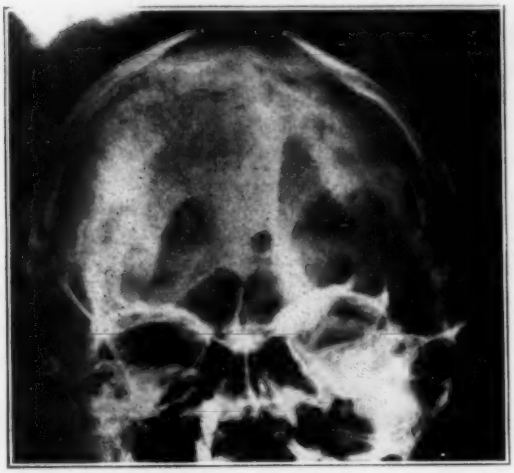

Fig. 2 (case 1).—Posteroanterior pneumoencephalogram, showing a huge porencephalic cyst in the left occipital region with ventricular communication.

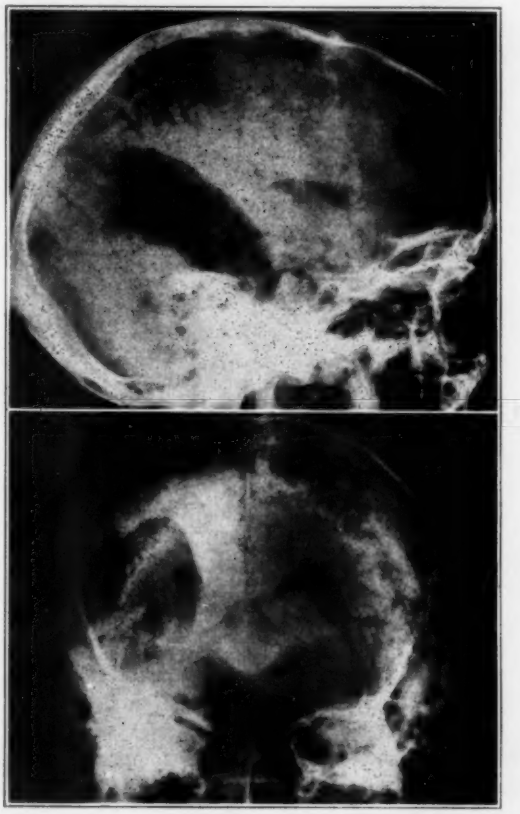

Fig. 3 (case 2).—Above, lateral pneumoencephalogram, showing large porencephalic cyst in the right occipitotemporal area. Below, posteroanterior view, revealing width of the cyst.

Case 2.—W. S., a white man aged 21, was admitted to the Illinois Neuropsychiatric Institute on Dec. 10, 1945, complaining of moderately severe bifrontal headaches for the preceding five years. The family history was noncontributory. At the age of 8 years the patient was said to have had many convulsive seizures, extending over a period of seven days. There had been no such episodes since that time. He stated that he had been "blind in the left eye" since the age of 8 years.

Physical examination revealed an entirely normal condition except for left homonymous hemianopsia without macular sparing. The usual laboratory examinations, including studies of the spinal fluid and serologic tests, gave normal results.

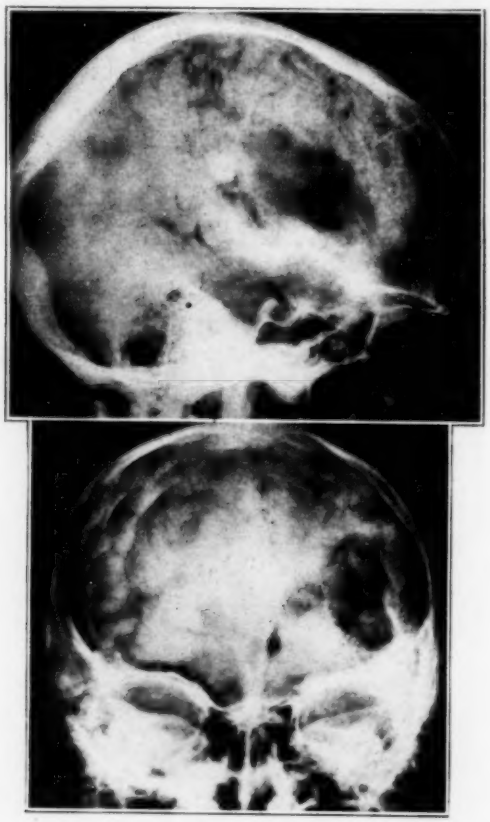

Fig. 4 (case 3).—Above, porencephalic cyst in the left frontocentral region, seen in lateral view. Below, cyst "budding" from the ventricle in anteroposterior projection.

Prominent asymmetry of amplitude was present in the electroencephalogram, with potentials of the lowest amplitude in the right temporo-occipital area (fig. 1 *B*). Pneumoencephalographic studies disclosed a huge, smooth-walled porencephalic cyst in the right occipitotemporal region in communication with the ventricle (fig. 3). Subarachnoid markings over the cyst and other constituents of the encephalogram were not remarkable.

Case 3.—W. T., a white youth aged 19, was admitted to the Illinois Neuropsychiatric Institute on April 10, 1946 because of convulsive seizures for the

previous six months. The family history was noncontributory. The patient is said to have sustained a birth injury, resulting in failure of development and weakness of the right side of the body. Fifteen months before admission he had fallen on ice, striking his head, and was rendered unconscious for twenty minutes. There was mild headache for the ensuing twenty-four hours but no other immediate sequelae. For six months prior to admission the patient had experienced infrequent convulsive seizures, with an aura of numbness and tingling in the right arm, jacksonian "march" on the right side with initiation in the hand, and then generalized tonus and clonus.

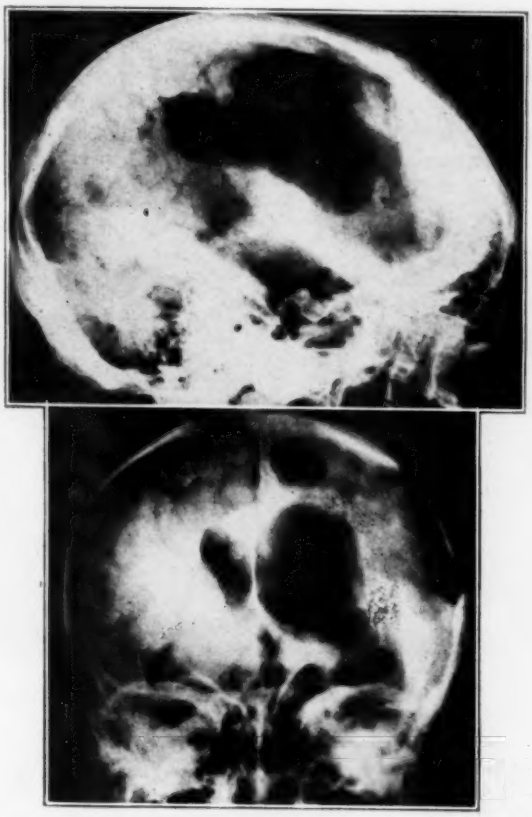

Fig. 5 (case 4).—Above, lateral view, showing porencephalic cyst in the left frontoparietal region. Below, anteroposterior view, showing extent of cyst and degree of ventricular dilatation.

The boy limped, with a hemiparetic gait. The right extremities, especially the arm and particularly the hand, were smaller than the left. There was typical right spastic hemiparesis without speech disturbances. The superficial modalities of sensation were impaired on the right side below the face, and there were complete atopognosia and astereognosia in the right hand. The usual laboratory examinations, including serologic tests and studies of the spinal fluid, gave normal results.

The electroencephalographic record revealed high voltage, 9 per second activity in all leads, with extreme asymmetry of amplitude between homologous areas in the two hemispheres; activity in the left hemisphere was of lower amplitude, and

the asymmetry was most evident in the parieto-occipital areas (fig. 1 *C*). A large, thin-walled porencephalic cyst was seen budding from the wall of the left lateral ventricle in the pneumoencephalogram (fig. 4). The cyst was present in the substance of the left frontal and central regions and was separated from the ventricle proper by a thin septum. There was slight shift of the ventricular system to the side of the cavity.

CASE 4.—F. E., a white man aged 26, was admitted to the Illinois Neuropsyciatric Institute on June 9, 1945 with a history of severe convulsive seizures since the age of 6 years. The past personal and family histories were noncontributory. At 7 years of age the patient had a particularly severe bout of seizures and since that time had been paralyzed on the right side. In 1925 exploration in the left parietal region had been made at another hospital, without any abnormality being encountered.

Physical examination disclosed a mentally dull and torpid person, with a scar in the left parietal region of the scalp. There were nystagmus on left lateral gaze and right spastic hemiparesis, including the face, with hyperreflexia and a Babinski

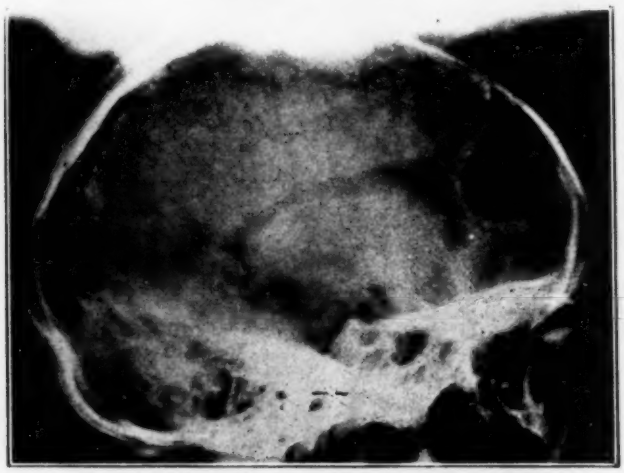

Fig. 6 (case 5).—Cyst of traumatic origin in right frontal area of the brain. The defect in the skull is visible.

sign on that side. The usual laboratory examinations, including serologic tests and studies of the spinal fluid, gave normal results.

The electroencephalographic record consisted of 6 to 9 per second activity in all leads, with extreme asymmetry of amplitude between the hemispheres, the left having the lower amplitude (fig. 1 *D*). During seizures there were many large 3 to 4 per second waves in the right hemisphere and fewer of these abnormal forms in the left hemisphere. Immediately preceding a clinical seizure there were generalized positive spike seizure discharges. The left lateral ventricle was greatly dilated, and there was a large porencephalic cavity in the left frontoparietal region of the brain (fig. 5). The cyst communicated with the ventricle, which was pulled toward it. A bony defect from the operative procedure overlay the dilated ventricle.

PSEUDOPORENCEPHALY

CASE 5.—R. Y., a white youth aged 17, was admitted to the Illinois Neuropsychiatric Institute on Feb. 18, 1946 with the chief complaint of convulsive seizures

for the previous four years. At the age of 4 years he had sustained a severe head injury in the right frontal region. This had been treated elsewhere by removal of bone and débridement of the underlying area of the brain. As the patient grew up, he became a problem child and eventually was arrested for stealing cars. For four years prior to admission he had had jacksonian seizures on the left, which spread to involve the entire body. There were a scar and bony defect in the right frontal region but no definite findings of neurologic deficit. The patient was a pathologic liar. Roentgenograms of the skull showed an oval defect in the right frontal bone and calcification in the subjacent portion of the dura or brain.

Electroencephalographic recording demonstrated a focus of 4 to 6 per second activity in the right hemisphere, most prominent in the right frontotemporal area (fig. 7 *A*). Pneumoencephalographic study showed a large cystic defect in the right frontal lobe (fig. 6). There were dilatation and traction of the ventricular system to the right.

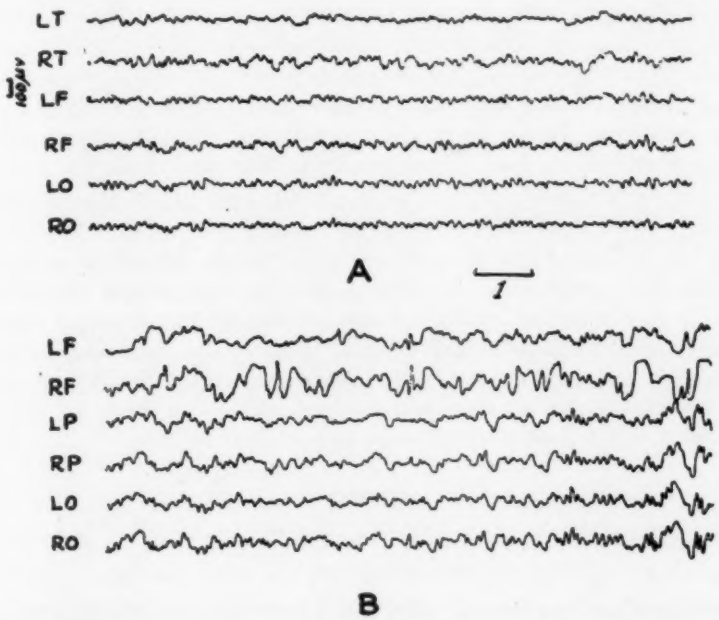

Fig. 7.—Electroencephalographic recordings in cases of post-traumatic cyst of the brain (pseudoporencephaly). *A* (case 5), discharge of slow waves from the entire right hemisphere, most prominent in the frontal lead. The cyst was located in the damaged right frontal lobe. *B* (case 6), focus of large slow wave and another of diphasic spike discharge localized in the right frontal area. The cyst was in the right frontal lobe.

Case 6.—C. W., a white youth aged 19, was admitted to another institution, electroencephalographic records having been taken at the Illinois Neuropsychiatric Institute. The patient had had generalized convulsive seizures and occasional cramping sensations in the extremities since the age of 9 except for a free interval between the ages of 16 and 18 years. Delivery at birth had been with forceps, and there was a scar in the right frontotemporal region.

The electroencephalogram showed low voltage, irregular activity with a focus of large slow waves and another of diphasic spike activity, sharply localized to the right frontal area (fig. 7 *B*). There were also generalized positive spike seizure

discharges. Pneumoencephalographic study revealed a large cyst in the right frontal lobe, without ventricular communication.

CASE 7.—C. J., a white girl aged 20, was admitted to the Illinois Neuropsychiatric Institute on Jan. 22, 1946 because of convulsive seizures and mental impairment, which had developed since an automobile accident two years previously. There were signs of pyramidal involvement on the right. Two foci of slow wave activity were seen in electrical tracings from the left hemisphere, one in the left frontal and another in the left occipital area. Both lateral ventricles were found to be dilated, the left more than the right; and there was a collection of subarachnoid air, which seemed to communicate with the left lateral ventricle posteriorly.

CASE 8.—H. B., a woman aged 30, was admitted to the Illinois Neuropsychiatric Institute on Feb. 28, 1945 with a history of convulsive seizures during the previous year. Physical examination demonstrated left homonymous hemianopsia with macular sparing, bilateral atrophy of the optic nerves and diminished visual acuity. The protein content of the spinal fluid was 71 mg. per hundred cubic centimeters. The electroencephalogram showed only slight slowing of activity, with a dominant frequency of 7 to 8 per second, and no evidence of focal or lateralized disorder. A ventriculogram revealed a large cystic cavity located paraventricularly in the right parieto-occipital area. Direct communication with the ventricle was questionable, the cyst apparently having been tapped directly (cloudy fluid obtained).

CASE 9.—J. S., a boy aged 7 years, was admitted to the Illinois Neuropsychiatric Institute on April 9, 1945 because of stupor and left hemiparesis. At the age of 8 or 10 months a cerebral abscess developed in the right occipital area as the result of perforation of the skull by a nail. The abscess had been drained, with improvement; but a year later hemiplegia and unconsciousness had developed suddenly. Significant physical findings were a pulsating mass in the right occipital region, left hemiparesis and mental retardation. An electroencephalogram was entirely normal. Pneumoencephalographic examination disclosed a cyst in the right occipital region, which probably communicated with the ventricle.

COMMENT

Jasper and associates [7] were first to correlate asymmetry of amplitude in the electroencephalogram with lesions of the brain, noting the presence of this abnormality in cases of subdural hematoma. Gibbs [8] stated that such asymmetry may be seen in a variety of conditions, including hematoma, cerebral aneurysm, concussion and lesions of the visual system.

We would add true porencephaly to the list of conditions productive of lateral asymmetry of amplitude in the electroencephalogram and further suggest an association of this type of electrical change with the undoubted vascular occlusive factor in the pathologic entity. Asymmetry

7. Jasper, H. H.; Kershman, J., and Elvidge, A.: Electroencephalographic Studies of Injury to the Head, Arch. Neurol. & Psychiat. **44**:328-348 (Aug.) 1940.

8. Gibbs, F. A.: Electrical Activity of the Brain, in Luck, J. M.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1945, vol. 7, pp. 427-454.

of amplitude has been noted in cases of homonymous hemianopsia [9] and in such circumstances has been thought to be due to interruption of the geniculocalcarine pathways. The visual projection system was certainly cut across by a porencephalic cyst in cases 1 and 2. In cases 3 and 4, however, the cyst lay frontally, and physical examination revealed no evidence of defect in the visual fields. In the experience of Strauss, Liberson and Meltzer,[9a] abnormally high degrees of asymmetry are found most frequently in cases of cerebrovascular lesions with involvement of one hemisphere. Sugar [10] observed a high incidence of asymmetry of amplitude in cases of migraine, the lower amplitude occurring on the side of the brain involved, as indicated by neurologic examination, and not necessarily on the same side as the headache. Apparently, then, interference with a major vascular supply to one side of the brain can produce lowering of amplitude of potentials from this side. It is possible that this electroencephalographic abnormality may be indicative of permanently deficient circulation in cases of true porencephaly.

In 3 of the 5 cases of pseudoporencephaly (cases 5, 6 and 7) foci of slow waves were manifested in the region corresponding to cerebral damage, with slowing of potentials from the rest of the hemisphere involved. In case 6, featured clinically by convulsive seizures, diphasic spikes were seen from the cortex overlying the cyst.

The only abnormality found in the electroencephalogram in case 8 was slight, general slowing. Records from case 9 (postinflammatory cyst) were entirely normal.

SUMMARY

The electroencephalographic findings in 9 cases of porencephaly, 4 of true porencephaly and 5 of pseudoporencephaly (post-traumatic or postinflammatory), are presented, with pneumoencephalographic confirmation of the diagnosis.

Asymmetry of amplitude of potential, the lower amplitude being on the side of the lesion, was a consistent finding in the cases of true porencephaly. In 2 of the 4 cases of this category the geniculocalcarine pathways were interrupted, but in 2 the cyst was present frontally and there was no evidence of involvement of the optic radiation. It is suggested that asymmetry of amplitude in cases of true porencephaly may be indicative of deficient cerebral circulation on the side of the lesion.

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9. (*a*) Strauss, H.; Liberson, W. T., and Meltzer, T.: Electroencephalographic Studies: Bilateral Differences in Alpha Activity With and Without Cerebral Pathology, J. Mt. Sinai Hosp. **9**:957-962, 1943. (*b*) Case, T. J.: Alpha Waves in Relation to Structures Involved in Vision, Biol. Symposia **7**:107-116, 1942.

10. Sugar, O.: Asymmetry in Occipital Electroencephalograms, Dis. Nerv. System **8**:141 (May) 1947.

Foci of slow waves localized to the part of the brain involved were found in the records of 3 cases of pseudoporencephaly (post-traumatic). Slowing of potential was manifest in tracings from the rest of the ipsilateral hemisphere. In 1 case of cerebral cyst (probably postinflammatory) the electroencephalogram showed only slightly slow activity, and in another (in which the cyst followed an abscess) the electrical records were entirely normal.

Electroencephalographic records were taken under the direction of Dr. and Mrs. Frederic A. Gibbs. Photographs were made by Mr. Willard Huntzinger.

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THE ELECTROENCEPHALOGRAM IN POLIOMYELITIS

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BECAUSE of the dearth of knowledge concerning metabolic changes caused by poliomyelitic infection of the central nervous system, it appeared of interest to study possible electrophysiologic alterations of the brain during the course of the disease. Electroencephalograms were therefore taken of rhesus monkeys and of guinea pigs with experimental infection with simian or murine virus. In addition, 17 persons with postpoliomyelitic paralyses were studied.[1]

Five monkeys were given intracerebral injections of simian virus into the right frontal area: Three received the RMV strain (0.5 cc. of viral cord suspension [1:10 or 1:100]); and 2, the Aycock strain (0.5 cc. of a 1:50 suspension). Two additional monkeys served as controls: One was given an intracerebral injection of 0.5 cc. of a 10 per cent Aycock cord suspension inactivated by boiling for twenty minutes, and the other received 0.5 cc. of isotonic solution of sodium chloride. Ten guinea pigs were infected with murine poliomyelitis virus (mouse-adapted strain of human MM poliomyelitis virus)[2]: Five received 0.1 cc. of a 1:10 viral mouse brain suspension intracerebrally, and 5 received 1 cc. of a 1:10 suspension intra-abdominally.

Electroencephalograms were taken from the experimental animals immediately prior to inoculation and at intervals during the course of the disease. A head

This study was aided by a grant from the Philip Hanson Hiss Jr. Memorial Fund.

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1. These patients were made available through the courtesy of Dr. Kenneth Landauer, Superintendent, New York State Reconstruction Home, West Haverstraw, N. Y.

2. Jungeblut, C. W., and Dalldorf, G.: Epidemiological and Experimental Observations on the Possible Significance of Rodents in a Suburban Epidemic of Poliomyelitis, Am. J. Pub. Health **33**:169, 1943. Jungeblut, C. W.: Serological Relationships Within the Poliomyelitis Group of Viruses, ibid. **34**:259, 1944; Studies in Rodent Poliomyelitis: VI. Further Observations on Interference Between Murine and Simian Strains of Poliomyelitis Virus, J. Exper. Med. **81**:275, 1945.

control apparatus attached to an animal board was used to immobilize the blindfolded monkeys. Curare ("intocostrin") was administered intravenously when necessary in a dose approximating 1 mg. per kilogram of body weight. Such small doses of curare were without significant effect on the electroencephalogram or the infection. This procedure had been previously carried out on monkeys in at least twenty control examinations. Blindfolded guinea pigs tied to an animal board remained sufficiently quiet to make the administration of curare unnecessary. Electroencephalograms were taken with a two-channel standard apparatus, utilizing a bipolar system of recording. A portable two-channel electroencephalograph was used to obtain tracings from the paralytic patients. The electrodes consisted of small needles firmly affixed to the scalp, over the corresponding prefrontal, motor and occipital regions of both sides of the head.

RESULTS

Monkeys.—In all 3 monkeys infected with RMV virus there was an elevation of temperature within seventy-two hours, with symptoms of paralysis appearing on the fifth or sixth day after inoculation. Death occurred between the ninth and twelfth days.

The 2 monkeys given injections of the Aycock strain exhibited an elevation of temperature on the fifth day after inoculation, with symptoms of complete paralysis on the eighth and the thirteenth day, respectively. The first monkey was killed, while the second animal died on the fourteenth day.

Electroencephalographic abnormalities were classified as slight, moderate or severe, depending on the frequency and incidence of slow activity, irregularity of pattern and amount of high voltage fast activity. Electroencephalographic tracings for normal monkeys had been previously described [3] and were used for comparison with the records of the infected animals. For the patients, electroencephalographic abnormalities were evaluated according to the standard criteria in current use, including the presence of delta activity, irregular features and high voltage fast activity.

None of the animals exhibited any definite electroencephalographic abnormality prior to the onset of fever or of clinical symptoms. However, coincident with the elevation of temperature on the third or fourth day, the 4 monkeys infected with the RMV strain showed a slight to moderate increase in the incidence and amplitude of alpha rhythm, and in fast activity. After the fifth or sixth day, whether the temperature remained elevated or not, there were a decreased incidence of alpha waves, a lowered voltage output, a relative increase in fast frequencies and an increase in the 6 to 8 cycle per second activity. The animals at this time exhibited generalized weakness and beginning paralysis. As the paralytic symptoms became more pronounced, there

3. Pacella, B. L.; Kopeloff, N.; Barrera, S. E., and Kopeloff, L. M.: Experimental Production of Focal Epilepsy, Arch. Neurol. & Psychiat. **52**:189 (Sept.) 1944.

were noted a greater incidence of slow activity, consisting chiefly of 5 to 7 cycle per second waves; random 4 cycle per second potentials; disappearance of alpha rhythm with a relative increase in the amount of fast activity, and a lowered voltage output. The 2 monkeys inoculated with the Aycock strain showed no definite changes in the electroencephalogram during the incubation period until paralysis set in. At this time the tracings revealed features similar to those noted in the animals inoculated with the RMV strain during the corresponding stage.

Electroencephalograms were taken daily on the 2 control animals for five days following intracerebral injection of inactive material, during which time they showed no symptoms. No abnormality or change in the electroencephalographic pattern was noted in the monkey given injections of isotonic solution of sodium chloride. The other animal showed lowered voltage output, decreased incidence of alpha rhythm and an increase in the amount of fast activity, which appeared twenty-four hours after the injection of heated cord suspension. A similar pattern was observed on the succeeding days of observation, but the changes never reached the intensity observed in monkeys inoculated with live virus.

The early appearance of increased amplitude and fast activity, associated with elevation of temperature in the preparalytic stage, may have been related to cerebral lesions resulting from progress of the virus from the intracerebral portal of entry to the spinal cord. Certainly the trauma of inoculation was not responsible for the electroencephalographic changes observed, since there was no evidence of a focal disturbance. These early changes, therefore, may carry some significance; however, somewhat similar tracings may be occasionally observed in the case of "normal" monkeys. The appearance of slow waves and the disappearance of alpha rhythm noted during the paralytic stage presented a definitely more abnormal picture.

Guinea Pigs.—Of the 5 guinea pigs given intracerebal injections, there was clinical evidence of infection in every case. Two animals died with flaccid paralysis of the hindlegs; 2 died without paralysis (which may have occurred but was not observed), and 1 had flaccid paralysis and recovered. Of the 5 guinea pigs given intra-abdominal injections, 1 died with paralysis; 1 died without paralysis, and 3 showed no clinical signs. In only 1 animal was a slight elevation of temperature noted.

Electroencephalographic tracings taken daily, beginning forty-eight hours before and continued for eighteen consecutive days after inoculation, failed to reveal any consistent or significant changes in pattern.

Paralytic Patients.—Electroencephalograms were taken on 17 patients convalescing from poliomyelitis, all of whom had exhibited severe

residual paralysis two and a half to fifteen months after the onset of acute symptoms. The tracings of 2 patients (respirator patients with bulbar paralysis) showed definite abnormality; those of 5, borderline abnormality (all were under 18 years of age), and those of 10, a normal pattern. However, the incidence of electroencephalographic abnormality in apparently normal persons might be of a similar order. This series is, therefore, too small to be significant for statistical evaluation. But the relatively large number of borderline tracings would seem to warrant further study of possible residual cerebral changes resulting from the infection. There was no correlation between laterality of peripheral paralysis and electroencephalographic findings in the cases of abnormal and borderline tracings. In all instances the electroencephalographic disturbance, when present, was of a diffuse nature.

COMMENT

The absence of any significant electroencephalographic abnormality during the period of incubation or the preparalytic stage in monkeys experimentally infected with simian poliomyelitis virus suggests that the electroencephalogram would be of doubtful diagnostic value in detecting poliomyelitic infection in man prior to the onset of paralysis. The electroencephalographic abnormalities observed in monkeys during the paralytic stage may have been due to encephalitic changes brought about by the artificial mode of inoculation. However, other factors, such as continued elevation of temperature and inanition with associated metabolic changes, may have contributed to the electroencephalographic disturbances even before notable encephalitic changes had occurred.

It was of interest to note that with guinea pigs given either intracerebral or intra-abdominal injections of the murine strain of poliomyelitis, electroencephalograms taken during the preparalytic, as well as the paralytic, stage showed no significant abnormalities. Clinically the guinea pigs showed no encephalitic symptoms but presented a picture of flaccid paralysis confined to the extremities.

Of the small series of convalescent patients examined, only 2 exhibited definitely abnormal electroencephalographic patterns. It is significant that both these patients had been maintained in the respirator for some time, and their illness could probably be diagnosed as polioencephalitis. Since classic poliomyelitis is essentially an infection with localization in the anterior horn of the spinal cord, the absence of electroencephalographic changes in most of our tracings, which were limited to the recording of cerebral activity, is not surprising. Whatever definite electroencephalographic disturbances were observed

appeared to be associated with the polioencephalitis caused by the experimental infection in monkeys or with the infrequent cases of bulbar involvement in man.

SUMMARY

1. No definite or consistent electroencephalographic changes which might indicate abnormal electrocortical activity were observed prior to the onset of fever or paralysis in monkeys given intracerebral injections of either the RMV or the Aycock strain of simian poliomyelitis virus. Abnormalities in the electroencephalogram appeared during the paralytic stage and became more conspicuous with the progression of symptoms. The electroencephalographic changes consisted chiefly in a progressive increase of slow activity, disappearance of alpha rhythm, a relative increase in the amount of fast activity and a lowered voltage output.

2. No electroencephalographic abnormalities were noted in guinea pigs given either intracerebral or peripheral injections of murine poliomyelitis virus in the presence or absence of paralytic symptoms.

3. Of 17 patients convalescent from poliomyelitis, all of whom had severe residual paralysis, 2 exhibited definite electroencephalographic abnormality and 5 showed a borderline disturbance. The remaining 10 patients had normal electroencephalograms.

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EFFECT OF CROSSING NERVES TO ANTAGONISTIC LIMB MUSCLES IN THE MONKEY

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CROSSING of nerves to antagonistic limb muscles or transplantation of the muscles themselves has been found to produce in the rat disorders of motor coordination directly correlated with the anatomic rearrangements. For example, transposition of the flexor and extensor muscles of the shank [1] or interchange of the nerve supply of these muscles [2] produced in each case a full reversal of the flexor-extensor movements of the ankle. A comparable reversal of motor action in the forelimb was shown to follow the crossing of nerves and the transposition of muscles acting on the elbow joint.[3] Sensory nerve crosses from one hindfoot into the contralateral hindfoot also were found to result in false reference of sensations and a maladaptive reversal of the withdrawal reflexes.[4] All these functional derangements persisted permanently in the rat without correction by reeducation.

Numerous clinical reports indicate, however, that man is capable of achieving motor readjustments considerably more complex than those called for by the foregoing nerve-muscle operations on the rat.[5] Consequently, it seemed imperative to conduct experiments of the sort

This work was done at the Yerkes Laboratories of Primate Biology as part of a project directed by Dr. Paul Weiss under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Chicago.

1. Sperry, R. W.: The Functional Results of Muscle Transposition in the Hind Limb of the Rat, Anat. Rec. (supp.) **73**:51, 1939; J. Comp. Neurol. **73**:379-404, 1940.

2. Sperry, R. W.: The Effect of Crossing Nerves to Antagonistic Muscles in the Hind Limb of the Rat, J. Comp. Neurol. **75**:1-19, 1941.

3. Sperry, R. W.: Transplantation of Motor Nerves and Muscles in the Forelimb of the Rat, J. Comp. Neurol. **76**:283-321, 1942.

4. Sperry, R. W.: Functional Results of Crossing Sensory Nerves in the Rat, J. Comp. Neurol. **78**:59-90, 1943; Fixed Persistence in the Rat of Spinal Reflex Patterns Rendered Extremely Maladaptive by Cross Union of Sensory Nerves, Federation Proc. **5**:98, 1946.

5. Sperry, R. W.: The Problem of Central Nervous Reorganization After Nerve Regeneration and Muscle Transposition: A Critical Review, Quart. Rev. Biol. **20**:311-369, 1945.

described for the rat on an intermediate form, such as the monkey. It was not intended in the present investigation to try to explore in full quantitative detail the capacities of the monkey for readjustment under such conditions. This would be a tremendous task, requiring, among other things, a preliminary analysis of normal muscle kinesiology beyond anything yet available, even for man. The object was, rather, to disclose, if possible, any basic and major differences in capacity for readaptation between the rat and the monkey that might appear under experimental conditions which were roughly similar, and to find out whether the results in the monkey would not approach closely those reported for man. It was hoped that such a comparison of the monkey and the rat might yield some clues to fundamental differences in organization of the central nervous system of these two forms which might explain in part the superior adaptability of the primates.

METHOD AND MATERIALS

The nerve branches to the primary flexor and extensor muscles of the elbow were dissected free, divided and cross united, so that the nerves were forced to regenerate into muscles antagonistic to those which they had formerly supplied. Nerves of the arm, rather than of the leg, were chosen because, other things being equal, motor readjustment should occur more readily in the arm.[5] Selection of these particular nerves and muscles acting on the elbow joint was made because of anatomic advantages for the type of operation involved, because the muscle function at this hinge joint is relatively uncomplicated and because the same nerves and muscles had been used in previous experiments on the rat.

After sufficient time had been allowed for nerve regeneration, the movements of the elbow were examined in natural and in trained activities, first for reversed movements and discoordination and later for evidence of correction of these abnormal movements. Because the animals soon learned to use the elbow joint by various trick methods without any active contraction of the test muscles, it became necessary to test coordination and to train for reeducation under special conditions in which such trick movements would not be possible. This was satisfactorily accomplished by making the monkeys reach through a metal tube for their food (figure). The tube was about the length of the monkey's upper arm and was large enough so that the fist partly closed over a small object could easily be drawn through it. The tube was mounted over a hole in the center of a large screen of hardware cloth, the mesh of which was too small to permit passage of the fingers but permitted the animal to see easily the object for which it was reaching. The screen and tube could be placed on the sides or on the top of the training cages. Pieces of food impaled on a stick were held outside the screen in such a position that they could be reached only if the monkey extended the arm into the tube all the way to the shoulder, with the elbow protruding slightly beyond the outer edge of the tube. In this position the elbow could be flexed and extended freely, but the upper arm and the shoulder were well stabilized in and against the tube. Elbow movement was easily observed under these conditions, and most of the trick movements depending on shoulder action, momentum or inertia of the forearm or special postures with respect to gravity were excluded. By holding the lure in different positions with respect to the end of the tube, by moving the lure after the animal had started to reach for it, and by using the tube

in vertical as well as in horizontal positions, one could test satisfactorily the monkey's capacity to flex and extend the elbow under a variety of conditions.

Use of the tube was begun shortly after recovery of function in the second arm in the bilateral cases. Approximately twenty trials per day for each arm were given through the first seven weeks. Thereafter the tests were administered over ten day periods at intervals beginning about once in every two months and increasing to once in six months at the end of the third year.

Observations were carried out over a total period of a little more than three years. Most of the data were obtained from 4 red spider monkeys (Ateles geoffroyi), 3 of them with nerves crossed in both arms and 1 with nerves crossed in one arm only. These full-grown animals had been kept in captivity at least six years prior to their use in these experiments. Additional results obtained on

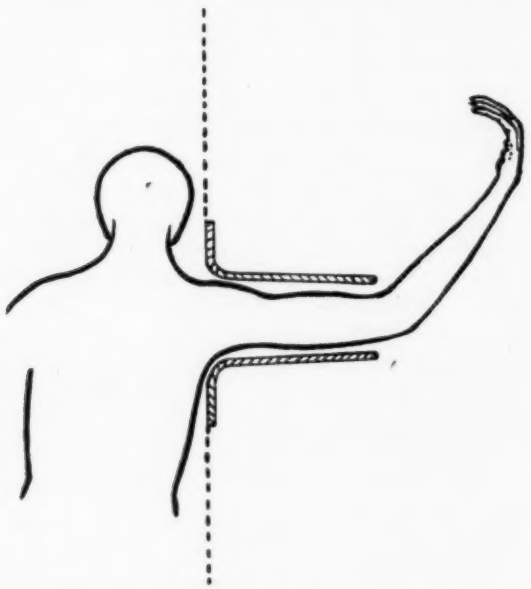

Diagram showing how elbow movements were tested by having the monkey reach through a short rigid tube.

2 macaques (Macaca mulatta) both operated on unilaterally, were in essential aspects similar to those obtained on the spider monkeys. The macaques were approximately 3 years old at the time of operation. They proved to be somewhat less satisfactory than the spider monkeys with regard both to the operation and recovery and to functional examination. One of the spider monkeys died at the end of one year and another at the end of the second year. The other 4 animals were killed about three and one-half years after their initial nerve-crossing operation. An additional spider monkey and a macaque, in both of which the elbow joint became ankylosed after operation, were discarded from the experiment.

The following control measures were taken: In all animals all extra muscles acting directly on the elbow joint were excised in order that their action might not counteract or obscure that of the test muscles. In the contralateral arm of

the spider monkey with unilateral nerve cross, nerve splices were made but failed to hold, and the nerves regenerated back into their proper muscle groups instead of into antagonistic muscles. Otherwise, this arm was operated on in the same way as in the other spider monkeys. It therefore made a good control and was used as such. To overcome the animals' tendency not to use an arm that had been operated on, the other arm was either similarly operated on, or, in the unilateral cases, paralyzed by repeated nerve crushing. Special care was taken throughout all tests to distinguish movement of the elbow caused by active contraction of the test muscles from movement produced by other methods. Biopsy was performed about two years after the first operation to check, by dissection and by electrical stimulation of the nerves proximal to the point of cross union, for the intended cross innervation as well as for any possible misregeneration of nerve fibers back into their original muscles. Again, when the animals were killed, the arms were dissected carefully, and electrical stimulation was employed to test once more for the existence of stray nerve fibers innervating their own, instead of antagonistic, muscles.

OPERATION PROCEDURE

The main trunk of the musculocutaneous nerve, which supplies the biceps and brachialis (flexor) muscles of the elbow, was dissected free and cut. Likewise, the nerve branches to the triceps (extensor) muscles were dissected free and cut at the same level. In freeing the extensor nerves, it was frequently necessary to split the nerve branches for several centimeters into their constituent loosely bound fascicles. This was done under a dissecting microscope with almost no difficulty in this region from intraneural plexuses. The central end of the musculocutaneous nerve was then united to the collected distal ends of the triceps nerves; conversely, the central ends of the triceps nerves were united to the distal end of the musculocutaneous nerve. Because there was no slack in the nerve lengths, the crossed stumps were fastened together, with only a small gap between them, by a single suture of fine silk through the epineurium. A tube of preserved monkey artery about 1.7 cm. in length was then pulled over each union. Finally, further to prevent any fibers from misregenerating into their original channels, a large sheet of allantoic membrane [6] ("insultoic membrane") was laid between the two splices.

The coracobrachialis muscle was excised, and its nerve was split proximally away from the musculocutaneous trunk, so that no nerve fibers to this muscle were included in the nerve cross. The end of this nerve was ligated and fastened proximally to prevent regeneration into the test muscles. The anastomotic nerve branch from the median nerve to the brachialis muscle was also severed, ligated and tied posteriorly, where it could not regenerate into its original muscle. The epitrochlearis (extensor) muscle and its nerve were left intact to help prevent ankyosis of the joint during the period of muscular paralysis. About six months after the primary operation this muscle was excised and its nerve ligated and fastened as far dorsally as possible. At the same time the muscles of the forearm which overlap the elbow joint and have their origin on the humerus, such as the brachioradialis, the pronator teres and the extensor carpi radialis longus, were excised to prevent their aiding in movement of the elbow. It has been shown that

6. "Insultoic Membrane" (Bauer and Black).

flexion of the elbow can be accomplished in man by some of these muscles after complete paralysis of the brachial flexors,[7] and such action is even more favored by the mechanical relations of these muscles in the monkey.

The method just described was used in crossing the nerves in the right arm of the 4 spider monkeys. An alternative procedure was used on the left arm of these animals and also on the left arm of the 2 macques as follows: The overlapping muscles of the forearm were excised in a preliminary operation about one month before the nerves were crossed. In the main operation, the central ends of some of the more proximal branches of the nerves to the triceps muscle were collected and crossed to the distal stump of the isolated nerve to the biceps muscle. The central end of the nerve to the brachialis muscle was crossed to the collected distal stumps of some of the more peripheral branches to the triceps muscle. When crossed in this way, the nerve stump could be joined with plenty of slack, and no silk suture was required. The nerves were trimmed to an appropriate length and joined in an arterial tube by a method similar to that advocated by Weiss.[8] The unused nerve stumps were ligated tightly and tied to tissues as far away from their original terminations as possible. The epitrochlearis muscle and nerve were left intact, to be excised about six months later. All operations were carried out with the subject under deep pentobarbital anesthesia.

No essential differences in the functional results were noted which could reliably be attributed to the different surgical methods of crossing. The essential effect of the operations by either method was to cause the flexor muscles of the elbow to become innervated only by what were originally extensor motoneurons, and the extensor muscles to be innervated only by flexor motoneurons such that a reversal of elbow movement should result in the absence of central nervous reorganization. Such terms as "reversed movement" and "reversed action" refer throughout to the unadjusted maladaptive action of the reinnervated muscles.

RECOVERY WITH REVERSED MOVEMENTS

Immediately after the operation on the right arm, the animals used the contralateral arm almost entirely. After the wound had healed, and while the nerves were still regenerating, the use of the experimental arm gradually increased, although the left arm remained dominant and preferred. The onset of recovery in the test muscles of the right arm was thus obscured by the tendency to use the normal (left) arm, as well as by the action of extrabrachial and antibrachial muscles left intact during the period of muscular paralysis to help prevent ankylosis of the joint. Removal of these extra brachial muscles again decreased the use of the right arm. Even when the overlapping muscles of the forearm had been freshly excised from the left arm, in the preliminary operation for the alternative surgical procedure previously described, the animal still preferred immediately afterward to use the left arm.

It was only later, after the nerves had been crossed or crushed in the contralateral arm, approximately eight months after the primary

7. Wright, W. G.: Muscle Function, New York, Paul B. Hoeber, Inc., 1928.

8. Weiss, P.: The Technology of Nerve Regeneration: A Review; Sutureless Tubulation and Related Methods of Nerve Repair, J. Neurosurg. **1**:400-450, 1944.

operation in all cases, that signs of function of the crossed nerves became apparent. When the animals were thus suddenly forced to use the arm with the cross innervated muscles in ways to which they had not been accustomed, they displayed reversed flexion and extension movements of the elbow. For example, in an attempt to extend the arm outward and forward horizontally for food, the forearm was, instead, flexed upward against gravity toward the chin. When the monkey tried to catch food impaled on the end of a stick, which was moved about slowly in front of the cage within easy reach, the elbow showed extension when flexion was called for, and vice versa. When the arm was being withdrawn through the wires of the cage, the forearm often flexed at right angles instead of straightening, thus becoming caught at the elbow. Efforts to straighten the arm only caused it to bend more acutely. Caught in this position, the animal would continue to tug and pull for some moments, until eventually the flexor muscles relaxed, the elbow straightened and the arm was pulled inside the cage.

Reversed movements of the sort just described appeared in all the 4 spider monkeys and in 2 macques, varying in intensity and frequency, however, in the different animals. They were most conspicuous in a spider monkey in which the muscles of the forearm and hand, as well as the test muscles of the upper arm, were paralyzed during the period of regeneration. This paralysis was probably caused by overstretching of the main nerve trunks, particularly of the radial nerve, at the time of operation. Consequently, this animal used the right arm hardly at all during the period of regeneration and, unlike the other animals, had had no practice in inhibiting the reversed action of the test muscles or in using the elbow passively during the preceding months.

In animals with bilateral crossed innervation the time of onset of functional recovery in the left arm was obscured in the spider monkeys mainly by trick methods of using the elbow joint passively and, in part, by preferential use of the right arm, which had previously been operated on. The animals were not suddenly forced to use the left arm in new ways, as had been the case with the right arm. There was plenty of time during recovery to adjust gradually to the postoperative conditions; consequently, reversed action was not seen in the left arm of these monkeys under natural cage conditions. It was only when they were forced to use the left arm in reaching through the metal tube, where the trick movements on which they had been relying were impossible, that reversal of elbow action on the left side became definitely apparent.

In 1 spider monkey recovery on the left side was exceptional in that no reversal of movement appeared under any conditions. On the contrary, well coordinated flexion and extension of the elbow in the proper direction occurred even in comparatively rapid movements. Biopsy, as well as examination after the animal had been killed, revealed that in this

instance the nerve crosses had not been successful. The nerve splices had pulled apart, and extensive misregeneration of nerve fibers into their original flexor and extensor muscle groups had taken place. Almost no crossed innervation was observed. The action of the reinnervated muscles of this limb therefore presented a good control for comparison with the function in those animals in which the nerve crosses had been successful.

On the whole, the reversed movements in the monkeys were much less conspicuous than had been the reversed limb movements in the rat after similar nerve crossing operations. In the rat the reversed responses were carried out with full intensity and scope persistently throughout all activities, the animals seemingly insensible of the reversal. In the monkey, on the other hand, the occurrence of a movement in reverse direction usually caused a break in the general activity going on at the moment. The erroneous reaction was halted and attention was turned to the abnormally acting member. After repeated attempts to improve the arm movement, the animal either succeeded somehow in getting the hand into a satisfactory position, or ceased trying altogether. As a result, and because of other factors to be mentioned, the reversed elbow movements tended to be weak in the monkey and in most instances to be brief or only incipient, without being carried through to completion.

The idea that central nervous reorganization to suit the new peripheral relations under such conditions occurs immediately and spontaneously, without any practice,[9] a view which has clearly been discredited in the case of the rat and lower vertebrates,[10] is also refuted by these results in the monkey. Not only did reversed movements appear during the early stages following nerve regeneration but, as will be described, the reversed action persisted in some instances for months, and even years.

After the early stages of recovery the test and observation program proceeded in an exploratory manner, with considerable irregularity and variation from animal to animal and from time to time. It would be prohibitive to recount in any detail the histories and specific findings for the individual animals throughout the three year period. An attempt is made, therefore to present the essential aspect of the results under the following topical headings, with examples illustrating the principal points in each instance.

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9. Marina, A.: Die Relationen des Paläencephalons (Edinger) sind nicht fix, Neurol. Centralbl. **34**:338-345, 1915. Bethe, A., and Fischer, E.: Die Anpassungsfähigkeit (Plastisität) des Nervensystems, in Bethe, A.; von Bergmann, G.; Einbden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1931, vol. 15, pp. 1045-1130. Goldstein, K.: The Organism, New York, American Book Co., 1939.

10. Sperry.[5] Weiss, P.: Self-Differentiation of the Basic Patterns of Co-Ordination, Comp. Psychol. Monogr. **17**:1-96, 1941.

TRICK MOVEMENTS AND SUBSTITUTIONARY REACTIONS

The monkeys were quick to find ways of using the experimental limb advantageously without contracting the test muscles. These compensatory, or "trick," methods of using the elbow passively were largely acquired early in the regeneration period, while the test muscles were completely paralyzed, and were then carried over with gradual improvement after the crossed nerves had regenerated. The ability to use the arm in such a way that the elbow would flex and extend passively as early as three weeks after the final removal of the extrabrachial muscles in the cases of bilateral crossed innervation was so good that a casual observer might well have failed to notice any motor disability. The efficiency with which the arms were used in regular cage activities suggested at first glance that complete central nervous reorganization must already have occurred, enabling the test muscles to contract in their proper action phase despite the abnormal innervation. With more careful analysis of the movements, however, it became apparent that this elbow action was not necessarily dependent on active contraction of the test muscles. In every situation observed, all flexor movements and all but a few rare extensor movements (see section on "Positive Readaptation") could be accounted for on the basis of other factors, such as gravity, inertia or secondary effects of muscles at other joints.

Extension of the elbow was easily achieved and maintained in most postures by the action of gravity. The forearm was simply allowed to fall loosely from the elbow into the extended position. In some postures the relative positions of elbow and forearm were adjusted by movement of the upper arm from the shoulder, so as to increase the effectiveness of gravity. At times the movement from the shoulder, combined with the inertia of the forearm, was sufficient to bring about extension of the elbow without the aid of gravity. When it was necessary to extend the arm upward against gravity, as in climbing, the elbow was usually extended first by gravity, and then the whole arm, straightly extended, was raised from the shoulder. At the same time the upper arm was properly rotated so that the weight and inertia of the forearm and hand tended always passively to extend the elbow, which, of course, would not bend beyond the straight position because of the structure of the bones and ligaments. With the upper arm in a horizontal position or at a downward angle, the flexed elbow could be extended simply by outward rotation of the arm from the shoulder, in which case the rotation of the upper arm swung the forearm into a position from which it was forced into extension by gravity.

Flexion of the elbow, which has to occur against gravity in most upright postures, was not achieved as frequently as extension. To flex the elbow upward to bring food to the mouth, the animal usually

propped the forearm against the knees in the sitting position. The elbow was sometimes flexed by gravity when the upper arm was raised. The spider monkeys frequently picked up food and put it in the mouth while hanging upside down from their tails. In this position the forearm hung vertically from the elbow and was flexed or extended passively as the elbow was raised or lowered. Occasionally the forearm was swung into a position of flexion by a flail-like motion. When the hand grasped the wires of the cage, flexion or extension of the elbow might occur, depending on movements of the upper arm and shoulder. Incidental and transient flexor, as well as extensor, movements of this sort occurred continually.

By these and similar methods adaptive flexion and extension of the elbow were achieved without active participation of the test muscles. These movements came to be performed quite smoothly, so that the monkeys appeared to get along in their natural cage activities without obvious motor impairment. Such movements tended to obscure whatever action of the test muscles may have been present and, at the same time, reduced the urgency of learning new motor patterns involving the cross innervated muscles.

Besides trick methods of using the elbow passively, many less direct substitutionary reactions were employed, such as increased use of the contralateral arm or of the ipsilateral shoulder and wrist to make up for the defective action of the elbow or use of the mouth, instead of the hands, to pick up food. Many of these substitutionary and trick adjustments probably required no learning at all, whereas others, particularly some of those involving movements of the elbow itself, undoubtedly required practice and learning in varying degrees. Adjustments of the sort described, involving shifts in the function of the normally innervated musculature, constitute the simplest means of readaptation to rearrangement of motor nerves. Even the rat showed some simple readaptation of this kind. The variety and scope of such readjustments, however, were obviously much greater in the monkey.

INHIBITION OF REVERSED MOVEMENTS

Complete readjustment in the action of abnormally innervated muscles requires, first, inhibition of old contraction patterns and, second, positive activation in new patterns. Both may be learned in a single step, or the two may be learned separately. Where learning of the two takes place independently, it is necessary to distinguish between them, because the type of central nervous adjustment may be quite different for the two processes. Undifferentiated inhibition of the arm muscles involves no more difficult an adjustment than would be necessary if the muscles had their normal nerve supply. To inhibit action at the elbow while, at the same time, retaining

movement of the wrist and shoulder is a more complex readjustment and apparently required some practice in the present cases. This still does not involve, however, the more specialized, and presumably more complicated, reversal of relations between the flexors and the extensors, as well as other arm and trunk muscles that would be required for positive readjustment of the contraction phase of the muscles. Also, the ability to halt reversed movements which are already under way ought to be distinguished from the ability to inhibit the initiation of reversed action. The interruption of adverse movements took place readily in most instances, apparently as a result of the visual and kinesthetic effects of the movement in reverse. It is the inhibition of the tendency to start reversed action that required practice and which is the main concern in the following discussion.

Many of the trick reactions mentioned in the foregoing section required that the reversed action of the test muscles be inhibited to permit loose passive movement of the elbow. These trick reactions were learned largely during the period when the test muscles were paralyzed and their active inhibition, therefore, not required. Later, however, when function was restored through reinnervation, active inhibition of the test muscles became necessary. The learning involved in this instance may have been aided considerably by the opportunity to acquire first the positive part of the coordination pattern while the test muscles were still paralyzed.

In some cases it was clear that the monkey learned to inhibit the reversed action of the test muscles rather quickly. For example, the reversed movements in the right arm that appeared immediately after the left arm was rendered useless did not last more than about three or four days in most of the animals. The reversals were most pronounced on the first two days and on the first trials of each test session on succeeding days. In 1 of the spider monkeys clear reversed movements appeared only in the first few attempts to elicit them on the first day and in the first trial on the second day. The animal refused to use the arm thereafter except in performances in which trick movements of various kinds were adequate. In another spider monkey, at the other extreme, the reversals remained conspicuous for about two weeks. The reversed reactions in this exceptional case were eliminated in large part by the end of the first month, but relapses remained common through the succeeding two months. This animal was the one which had had no practice in the use of the arm during the period of nerve regeneration because of temporary paralysis of the muscles of the forearm and hand. The notable difference between this animal and the others indicated that the more rapid inhibition of reversed elbow movement in the other animals could be ascribed to the practice which they had already had in the preceding months, both before and after the reinnervation of the test muscles.

The disappearance of reversed elbow movements after a short learning period under the foregoing conditions does not imply the onset of correct reactions in the test muscles. At first the animals simply refused to employ the arm in circumstances in which it had moved in reverse direction. Later they hesitantly began to use it, gradually dropping out all reversed action at the elbow. This inhibition of reversed action merely made it possible to use the joint passively by various trick methods of the kind described in the preceding section.

In the special test situation in which the animals were forced to reach for things through a tube, inhibition of reversed movements came somewhat more slowly. Under these conditions it was not so easy to resort to trick movements, nor was there as much opportunity for practice. In the animal which learned most rapidly it was almost two weeks before the reversed movements were clearly beginning to be inhibited. With most of the animals it was more nearly three to four weeks before they had begun to learn to inhibit reversed action of the elbow in simply reaching for a stationary lure. The reversed action thereafter became less frequent and extensive, but obvious reversals were still not uncommon as late as six, eight, nine and sixteen months after training had been started in different cases. Improvement took place in both arms with about equal speed in 1 of the 3 monkeys with bilateral crossed innervation. In the other 2 monkeys the right arm improved more rapidly than the left, especially in the early stages of training. This was to be expected, for the right arm had recovered first from the operation and had had more practice than the left. The superiority of one side over the other could be taken as evidence either that there was lack of transfer of learning from one side to the other or that the motor coordination used on the two sides was somewhat different.

One spider monkey was exceptional in that it persistently continued to exhibit predominantly reversed action throughout two and one-half years without evidence of any appreciable improvement by learning. This animal was unable to obtain a lure even in a position in which it was merely necessary to relax the test muscles so that the forearm would fall into flexion passively by its own weight. Under these conditions, with the animal obviously straining with full effort to flex the elbow downward, the forearm remained stiffly extended against gravity. Learning appeared abruptly toward the end of the second year of training in this case, and, once started, it proceeded fully as rapidly as in the others. This exceptional monkey was the one in which the left arm was the control. Its slowness in learning may, therefore, have been due to the fact that it used the more proficient control arm regularly and did not give practice to the experimental arm.

The steps by which the different animals learned to reach through a horizontal tube and flex the elbow downward 90 degrees were sur-

prisingly similar, and in some respects not unlike the method of learning described by Weiss and Brown [11] after muscle transplantation in man. At first there was only stiff extension of the elbow straight outward against gravity, and after a moment the monkey usually stopped trying to flex the arm and withdrew it from the tube. With sufficient hunger the animal persisted in its efforts for a longer time, in the course of which there were momentary relaxations of the extensor muscles, which may possibly have been accompanied with active contraction of the flexor muscles. In any case, the result was short, sudden flexor movements of the elbow imposed on the predominant extension. These sudden, almost spasmodic, flexor movements were then increased in frequency and extent during the second and third weeks of training, the forearm swinging up and down through an angle of 90 degrees. At the bottom of the downward stroke the hand and fingers came in contact with the lure, but at this stage of learning the hand movements were not coordinated with the elbow movements, and the lure was usually missed because the fingers failed to close at the proper moment. Eventually, after two or three months, the monkey managed to inhibit the predominating extension, so that the forearm, after it had fallen into the flexed position, was not immediately jerked back into extension. There was then time for the fingers and hand to grope for and grasp the lure. At the end of three years the downward flexion of the forearm and the opening and closing of the hand had become coordinated into a single movement, but at best it still lacked in all cases the speed and sureness of the same movement in the control arm.

There was thus a striking difference between the monkey and the rat with respect to the inhibition of reversed movements. In the rat the reversed movements persisted indefinitely. In the monkey, on the contrary, they were quickly halted and inhibited. In only 1 monkey, under particular conditions already described, did the reversal persist in a manner at all resembling that in the rat. This was in an animal which had used its arm comparatively little because of the proficiency of the contralateral arm.

POSITIVE READAPTATION

Readaptation went further than the mere acquisition of various trick movements and inhibition of reversed action. Positive readjustment in the active contraction of the muscles supplied by the crossed nerves was eventually achieved to some degree in all animals. It generally came later and more slowly than inhibition of reversed patterns, although in some reactions the two occurred simultaneously. There was con-

11. Weiss, P., and Brown, P.: Electromyographic Studies on Recoordination of Leg Movements in Poliomyelitis Patients with Transposed Tendons, Proc. Soc. Exper. Biol. & Med. **48**:284-287, 1941.

siderable variation in the time required for such readjustments to occur in the various animals and in the level of efficiency finally achieved. Such differences seemed best ascribed to accidents of learning.

Adaptive extension of the elbow against gravity appeared in the right arm of 2 spider monkeys and in the left arm of 1 macaque when they were induced to reach for food in the early months following completion of nerve regeneration. This active extension of the elbow in the correct direction, however, was slow, weak, accompanied with pronounced tremors and generally rather inefficient in all cases. The monkeys were observed to use this extension of the elbow only when food was offered in such a position that it could not be reached otherwise. They preferred to extend the elbow passively and then raise the whole arm from the shoulder whenever possible. Along with these correct extensor actions the animals exhibited as well flexor and extensor movements in reverse in other performances.

When biopsy was performed, it was observed that some extensor fibers had escaped and misregenerated into the extensor muscles in the animals that had first shown adaptive active extension. Similar misregeneration was also observed, however, in 2 other animals which had not shown these early extensor movements. The extent of this unintended reinnervation of the original muscles appeared to be quite small, for only a small twitch of the triceps muscles was elicited with maximum electrical stimulation. In only 1 case was the contraction strong enough to cause a short extensor movement of the elbow. Because the extensor nerves were numerous and some of them very fine, and because the proximal nerve stumps were almost surrounded by extensor muscles, it was difficult to prevent at least a few fibers from escaping back into the extensor muscles. An effort was made at the time of biopsy to search out, cut and ligate all these misregenerated fibers. Afterward, the animals were still able to extend the arm actively at the proper time, however, indicating that by this stage of recovery, at least, the adaptive extension involved function of the nerves successfully crossed. It remained uncertain whether or not the early extensor movements had been effected by the misregenerated nerves.

There was much less chance for the flexor nerves to regenerate back into their proper muscles, and no misregeneration of this sort was seen at biopsy among the experimental animals except in 1 monkey, in which a fine thread of fibers had misregenerated from the median nerve into the brachialis muscle. The function in this case was not significantly different from that in the others. The following data on positive readaptation on the flexor side are, therefore, not complicated by the presence of unintended nerve regeneration.

There was no evidence of active adaptive flexion of the forearm in any of the animals in the course of ordinary cage activities during the

early months following the completion of nerve regeneration. It was not until the monkeys had been trained for varying periods to reach through the tube that the first signs of adaptive flexor action appeared. All the animals eventually learned to flex the forearm against gravity in this situation. At first the flexor movements in the proper direction occurred accidentally and were peculiarly sudden and spasmodic. For example, in an attempt to flex the forearm upward with the upper arm stabilized horizontally in the tube, the predominant reversed extension was occasionally broken by a sudden upward flexion of the forearm, which immediately was snapped back into extension. There seemed to be little or no control over these early accidental movements in the proper direction. Even when the arm flexed sufficiently for the hand to come in contact with the lure, the lure was not grasped. It was as though the correct movement had caught the monkey by surprise, so that it was not prepared to grasp with the hand at that moment. In time the animal learned to grab at the lure at the height of these sudden upward swings. Later still, some control was acquired over the flexion itself, so that the movement could be made more slowly and steadily, allowing time for the wrist, fingers and angle of the forearm to be shifted in adaptation to the particular position of the lure.

In the case of these active flexor movements against gravity, the time required for learning was not appreciably different from that involved in flexion with gravity, where only inhibition was required. By the end of a month the monkeys, with 1 exception, had clearly begun to flex the elbow when flexion was called for, 90 degrees and sometimes more. They were not able to do so consistently and the movements were still rather spasmodic and poorly controlled, but there was unmistakable advancement over the reactions made during the first week of training. The final step to be learned in this performance by most of the animals was the coordination between finger and elbow movements. A point was reached at which the elbow could be flexed properly to bring the hand into the vicinity of the lure and held there, but as soon as the fingers were opened and an attempt was made to grasp the lure, the elbow simultaneously extended, carrying the hand out of reach. By the end of eighteen months this difficulty was overcome. The animals were able to flex the forearm upward to an angle of 90 degrees and to hold the flexed position while the lure was grasped with the fingers. The movements still showed pronounced tremors in 2 monkeys and all the animals had occasional relapses in which the elbow would extend repeatedly when flexion was attempted. In these particular conditions, apparently, the active contraction against gravity was learned about as readily as the downward movement with gravity. With regard to the relative speed of learning on the two sides in the 3 bilateral preparations, the conditions paralleled those already given

for learning to flex the arm downward. Thus, in this respect, also, the learning processes involved in flexing downward with gravity and in flexing upward against it were closely related, suggesting that the coordinations were not much different in the two situations.

The 1 exceptional animal mentioned had not progressed at the end of eighteen months beyond the point where the forearm displayed repeated spasmodic flexions to about 40 degrees at most, with the hand attempting to grasp the lure when it was held within this range. Often the hand failed to close on the lure even when the palm or volar surface of the fingers made contact with it. This was the same animal which had not even learned by this time to relax the brachial muscles so that the forearm could flex downward passively by its own weight. Ability to flex the forearm was acquired suddenly during the second day of a training session near the end of the second year. For the first time the monkey managed to flex the forearm upward a full 90 degrees. The capacity to flex the elbow was retained on immediately succeeding trials in horizontal and downward directions, as well as in the upward direction. In the course of the next two days the flexor movements, which first had been abrupt, spasmodic jerks, became slower and steadier. Positive readaptation in this instance, then, was established directly, without an intermediate stage of indifferent inhibition. As mentioned, this animal in which learning was exceptionally retarded was the one whose other arm served as a control, and it is probable that the delay in learning was causally related to the fact that the experimental arm did not get as much practice as in the other animals.

In the left arm of 2 of the spider monkeys upward flexion of the forearm was conspicuously associated with pronation of the hand. If the hand was in a position of supination, the elbow extended when flexion was attempted. As soon as the hand turned into pronation, the elbow flexed. If the elbow were already in the flexed position and the hand became supinated in an attempt to grasp the lure, the elbow immediately extended, carrying the hand in a reverse direction away from the lure. This association of pronation and supination with flexion and extension of the elbow was rather strict in the first stages of learning but had almost disappeared by the beginning of the third year.

When the lure was moved slowly about with erratic changes in direction after the animal had started to reach for it, the monkey was quite unable to follow it in the early training sessions. Reversed flexor and extensor action at the elbow caused a great deal of excess waving of the arm, with overreaching and false starts, until the monkey either chanced to hit against the lure or ceased trying altogether. Eventually the monkeys all acquired the ability to make their movements predominantly in the correct direction, but complete elimination of reversed action was never achieved in any case. The animal in which the learn-

ing of simple flexion had been exceptionally delayed was greatly retarded in this performance also. Even in the animal with most advanced recovery, the movements after three years remained abnormally slow and hesitant, with pronounced tremors, overreaching and starts in the wrong direction. By contrast, the control arm under similar conditions could immediately snatch a piece of food off the end of the moving stick with no difficulty whatever. Even in simple flexion or extension of the arm to reach a stationary object, there remained to the end an obvious contrast between the quick, sure movements of the control arm and the slow, uncertain movements of the experimental arm.

In their regular cage activities the monkeys continued throughout the three year period of observation to rely primarily on trick methods of using the elbow. However, by the end of two years they had all acquired at least a few movements which involved active participation of the test muscles. For example, in certain positions in which they scratched themselves active elbow flexion against gravity was required. In reaching underneath the cage walls to steal food from neighboring cages, an awkward action in which trick movements were of little help, the animals managed to extend and flex the elbow without aid of gravity. On rare occasions, especially when the animals were competing for food, they would sometimes pick up food and lift it directly to the mouth by flexing the elbow against gravity without bothering to use the knee as a prop. The natural reactions of this kind in which adaptive function of the test muscles was involved were few. Those used most frequently were carried out in a smooth, and apparently automatic, manner without hesitation or tremors, such as were present in the specially trained movements with the tube. The better quality of coordination in these common cage activities may be attributed to the much greater amount of practice which they received. Vision was used to help guide the elbow movements to a large degree, but it was not necessary. The scratching reactions were regularly carried out without visual aid. Also, in reaching through the tube, it was common for the monkeys, after locating the position of the lure visually, to turn the head sideways in the act of reaching, so that the eyes could not be used further in guiding the arm movements.

GENERALIZATION AND TRANSFER OF LEARNED REACTIONS

It is theoretically conceivable that, having once learned in a particular performance to flex the elbow with cross innervated muscles, the animal might thereafter be able to flex the elbow properly in any other performance. On the other hand, it is possible that flexion and extension of the elbow would have to be relearned separately for each performance. The actual results came much nearer the latter extreme than the former. There were a number of instances in which the learning

clearly failed to be transferred spontaneously from one performance to another. For example, after animals had learned to inhibit reversed flexion when trying to extend the arm horizontally for food in front of the cage, they again exhibited reversed flexion when induced to reach under similar conditions through the side of the cage or from a height or posture different from that in which the original learning had occurred. Most of the animals had learned to inhibit reversed action of the test muscles before they were tested with the tube. When these tests were started, however, the same reversal of elbow movement reappeared, and its inhibition had to be learned again in the new situation. The animal which was exceptionally slow in learning to flex the elbow when reaching through the tube had been able to flex the elbow to scratch itself or to pull food through the cage wires for almost a year before it finally learned to flex the elbow similarly in the tube situation. There was, thus, a striking lack of transfer in many instances.

If the learning process involved rearrangements in the relationships, of the primary or secondary neurons with the spinal centers, as contended at times in the past, one would expect a complete transfer of learning from one performance to all. Once the basic relationships of the spinal limb centers had been readjusted, the adjustment should be effective for all limb movements. The fact that learning to flex or to extend the elbow in one situation did not necessarily become generalized for other performances indicated that the neural readjustment was not localized in the spinal centers but involved, instead, reorganization of cerebral processes specialized for the different performances.

EFFECT OF PENTOBARBITAL AND CORTICAL LESIONS

To see whether it would cause a breakdown in the new coordination patterns and a return of reversed movement, 2 of the animals were given a three-fourths anesthetic dose of pentobarbital sodium subcutaneously. This was done on two separate occasions near the end of the third year. When the monkeys had reached a stage at which they were beginning to be unsteady in their movements, the elbow coordinations were tested. In 1 case there was a definite increase in the amount of reversed action at the elbow, but not a complete breakdown of the adaptive movements. It looked as though the animal was quite indifferent, and not concentrating on the arm movement as much as usual. In the second case the drug seemed to improve the elbow coordination. Under the influence of pentobarbital, this animal used the elbow more frequently than usual and with less tension. The animal seemed to be better relaxed, and the arm did not show the stiff extension which characteristically occurred under normal training conditions when flexion was attempted. This animal was the exceptionally slow learner. Apparently, the relaxation produced by pentobarbital may have either a bene-

ficial or a deleterious effect, depending on whether the animal in normal circumstances is sufficiently or too little relaxed for optimal performance.

An attempt was also made to produce a relapse into reversed movements by making lesions in the cerebral cortex. In 1 animal bilateral destruction of arm area 6 and the anterior half of arm area 4, as given on architectonic charts, caused so severe a paralysis that meaningful tests could not be made. In 2 additional animals the frontal lobes were removed bilaterally, and in another operation extensive lesions were made in postcentral arm areas 1, 2, 5 and 7. In 1 of these animals the frontal lobes were removed first, and in the other the postcentral lesions were made first. In both animals the removal of the frontal lobes produced a temporary increase in the amount of reversed action, from which there was recovery by the end of two weeks. The postcentral lesions made it difficult for the monkeys to aim the arm movements accurately. They had great difficulty, for example, in getting the hand into the tube. In the flexor-extensor movement of the elbow, however, there was no sign of increased reversal. The results showed that the habit was not dependent on the frontal lobes and suggested that kinesthetic stimuli from the arm were not of major importance in the control of the adapted elbow coordinations.

ANATOMIC CHECKS

When the animals were killed, the brachial nerves were dissected free, with the use of anesthesia, and stimulated electrically to test for the presence of nerve fibers innervating their original muscles. All animals seemed to be free of such fibers except for the control monkey. Apparently, all unintended regeneration that had been present was successfully eliminated in the biopsies earlier in the experiments. The brachialis muscle in 1 of the macaques was not completely atrophic but did not contract to stimulation of any of the flexor nerve trunks. In the right arm of 1 of the spider monkeys the triceps muscles were not more than one-eighth their normal size. In the left arm of another spider monkey only the medial head of the triceps muscle was reinnervated, the other parts being atrophic. The test muscles were otherwise in good condition and ranged roughly from about two-thirds normal to normal in size. Stimulation of the nerves proximal to the region of cross union produced quick, vigorous responses of the forearm in the direction opposite the normal. Further dissection of the nerves disclosed nicely crossed nerve connections with no further evidence of unintended regeneration. Microscopic examination of samples of the crossed nerves from 3 of the animals showed rich reinnervation of the distal nerve stumps. In the region of the scar the fibers followed rather erratic courses, but this was not of much consequence because the motor components of the nerves were functionally homogeneous.

COMMENT

When the foregoing results are compared with those obtained after the interchange of limb nerves in the rat, the superior readaptive capacity of the monkey is very apparent. The monkey is quick to halt reversed movements, as well as to find new ways of accomplishing various acts without using the abnormally innervated muscles. Positive correction in the contraction phase of the test muscles was also eventually achieved. The active coordination of the cross innervated muscles became smooth and automatic in the course of two years in some reactions which received constant daily practice in regular cage activities. The rat, on the other hand, was found to repeat the reversed movements indefinitely without correction and even without inhibition of the reversed action.

Regarding the problem of the neurologic basis of the monkey's superiority, there are a number of known factors that appear significant. First, there are the obvious advancements in the structure of the primate nervous system and its associated end organs,[12] of which the following may be listed as particularly pertinent: (*a*) the more highly developed sensorimotor cortex; (*b*) the more elaborate connection systems between the spinal limb centers and the higher levels of the brain, especially the corticospinal tracts and the dorsal funiculi and medial lemniscus system; (*c*) the increased ratio of sensory to motor fibers in the limb nerves; (*d*) the increase in number and differentiation of sensory nerve terminations in the skin, tendons, muscles and joints, and (*e*) the mechanical arrangement of the muscles and skeleton of the primate limb so as to permit a much greater range of variation in limb movements than is possible in the rat.

To these anatomic differences may be added a number of functional differences which showed up in the course of the experiments. First, the monkey appears to have a greater capacity for detecting the presence of abnormal movements and for sensing in some degree the location and nature of the motor difficulty. Whereas the rat may continue indefinitely to repeat without modification a movement in reverse and seems meanwhile to remain oblivious of the reversed action, the monkey indicates by its behavior a more direct awareness of when and where an error has been made. The beginning of a single movement in reverse is often sufficient in the monkey to disrupt the activity going on at the moment. Sometimes it appears that the monkey stops and concentrates its attention on the member that is at fault. This is particularly true

12. Ariëns Kappers, C. U.; Huber, A. C., and Crosby, E. C.: The Comparative Anatomy of the Nervous System of Vertebrates, Including Man, New York, The Macmillan Company, 1936.

when the limb is being used in a "voluntary" manner, as in reaching for or handling something.

This difference in capacity for perceiving the presence and location of adverse reactions is correlated with a second factor, namely, a difference in the way the animals naturally use their limbs. The rat is not adapted, like the monkey, for finely controlled, deliberate, delicate movements of individual limbs or separate segments of the limbs, as in manipulation. It is in movement of this sort that learning appears to occur most readily. Both the aforementioned factors are therefore probably important in the monkey's superiority: the ability to make discriminate voluntary movements of individual limbs and parts of the limb, and also the perceptual capacity to attend to such specific movements, to guide them and to note their effects.

There is a third possible factor, not unrelated to the two already indicated, which may also account in part for the monkey's quicker detection and inhibition of reversed movements, namely, a greater dependence of the motor control of limb movement on sensory cues, especially those originating within the limb itself. In the rat the adverse sensory effects resulting from movement of one joint in reverse is not sufficient, as in the monkey, to disrupt the motor sequence. The aforementioned three factors together make the reversed action of cross innervated muscles inconspicuous in the monkey as compared with the rat.

Another factor of significance is the greater diversity of limb movement present normally in the monkey. The rat tends to use a limb as a whole in a stereotyped manner, with relatively few variations of the coordination pattern. In the monkey, however, the various limb segments may act differentially, being flexed, extended or rotated in various combinations, with a large variety of possible permutations of the coordination pattern. Because dissociation in the action of cross innervated muscles is a prerequisite of readaptation, the monkey, with a high degree of such functional dissociation already present normally, has a great advantage over the rat, in which the limb muscles are more rigidly bound together in restricted functional associations.

The ability to activate the test muscles in many different combinations with other limb muscles opens the possibility for their activation in the new proper combination to suit the crossed innervation. It is necessary in learning a new motor skill to achieve the new coordination a first time, whether by directed effort or by accidental blunder. Once made, the new coordination can be reenforced by further repetition and practice. In the rat the proper coordination was apparently never achieved, even a single time. The limb always worked in the old patterns, without any trial variations. It remained questionable whether the motor system of the rodent is so organized as ever to permit the

required reassociation of muscle function. The ability of the monkey to make diversified trial coordinations would seem to be an extremely important item.

Another factor favoring motor reeducation in the monkey is the fact that learning plays a much greater role in the original ontogenetic acquisition of motor coordinations. The monkey to start with is, therefore, already more experienced than the rat in learning new arm coordinations. Furthermore, it is to be expected that coordinations established largely by learning in the first place will be more easily reorganized by the learning process than those built into the system by processes of growth and maturation.

In addition to the specific items aforementioned, there remains supposedly a central intelligence factor involving the general organization and differentiation of the brain, regarding which little can be added on the basis of the present experiments.

The foregoing advancements ascribed to the monkey are, of course, to be found also in man, even better developed in most instances. Certainly, man would be far superior to the monkey in the early stages of reeducation, i. e., in the detection and understanding of the motor difficulty and, consequently, in the guidance of corrective training. In any attempt to extrapolate to man from these results in the monkey, one must remember that most of the cases of nerve crossing and nerve regeneration, as well as those of muscle transposition, met in the clinics require a different and more complicated type of motor reorganization than that demanded by the clearcut reciprocal cross of these experiments.

SUMMARY

1. In 4 spider monkeys (3 with bilateral and 1 with unilateral crossed innervation) and in 2 macaques (both with unilateral crossed innervation) reversed movements of the elbow followed the surgical interchange of the nerve connections of the elbow flexor and extensor muscles with removal of all other muscles acting on the joint.

2. These reversed movements were quickly abandoned in ordinary cage activities, and a large variety of "trick" or compensatory reactions were rapidly acquired as substitutes for the abnormal action of the test muscles.

3. After about two months' practice at most, the reversed movements could be elicited only by using special measures to force the animals to use the elbow under conditions in which trick movements were excluded and in which there had not been previous opportunity to learn to inhibit the reversed action.

4. Readaptation went farther than the development of trick movements and inhibition of reversed action. Positive readjustment in the

function of the test muscles was eventually achieved in all cases, until the monkeys could actively flex and extend the elbow in an adaptive manner. A few of these corrected reactions which received constant practice in natural cage activities seemed to be as smoothly coordinated at the end of three years as the same movements in a control case after a similar operation but in which the nerves regenerated into their original muscle groups.

5. Correct use of the cross innervated muscles learned in one performance was not transferred automatically to all other performances. Lack of such transfer was strikingly apparent in a number of instances.

6. Reversed action at the elbow persisted throughout the three year course of the experiments in certain performances which received comparatively little practice.

7. The new motor coordinations survived bilateral frontal lobectomy combined with extensive bilateral lesions in the cortical arm areas 1, 2, 5 and 7.

8. Comparison of the present results with those of similar surgical operations carried out previously on the rat indicated throughout a marked superiority of the monkey. Some of the known factors, anatomic and functional, contributing to this readaptive supremacy of the primate nervous system are discussed.

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INNERVATION OF THE CHOROID PLEXUS

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THE STUDY of the innervation of the choroid plexus is attended with great technical difficulties, explaining the paucity of investigations on this subject. Isolated notes on the nerve supply of the choroid plexus are found in the works of older authors. As far back as 1874 Benedikt [1] identified nerve fibers in the choroid plexus of the fourth ventricle. He used carmine staining. These fibers were rami of the tenth nerve and originated in the cells of the nucleus ambiguus. Benedikt named these fibers "the thirteenth nerve." His observations were confirmed by Bokhdallek and Purkinje. Bkhnenek described nerve plexuses around the vessels of the "paraphysis" of the frog. He was able to trace the course of the fibers from these plexuses to the choroid plexus of the lateral ventricles. Findley drew attention to the presence of sympathetic nerve fibers in the choroid plexus of man and cattle. Together with Studnitska, he discovered ganglionic structure in the choroid plexus. According to Findley, the sympathetic fibers of the choroid plexus arise from the internal carotid plexus, and he denied the possibility of a different origin.

SURVEY OF LITERATURE

In 1911, Khvorostukhin, by using a methylene blue stain, discovered in the choroid plexus of various mammals nerve plexuses consisting of thick medullated and thin nonmedullated fibers. He was able also to trace the branching from thick nerve fascicles of thinner fibers, from which, in turn, still thinner fibers branched off. Subepithelial plexuses of thin nerve fibers were also identified by Khvorostukhin. In exquisitely stained slides, he observed how rami of a subepithelial plexus gave off thin nerve fibrils, which terminated on the surface of the epithelial cells. Finally, he discovered nerve fibers and their plexuses around blood vessels.

Stöhr [2] described the innervation of the cerebral membranes and made accurate notes on the innervation of the choroid plexus. He made

1. Benedikt, M.: Ueber die Innervation des Plexus choroideus inferior, Virchows Arch. f. path. Anat. **59**:395-400, 1874.

2. Stöhr, P.: Ueber die Innervation des Plexus choroideus des Menschen, Ztschr. f. d. ges. Anat. (Abt. 1) **63**:562-607, 1922.

his studies on fresh human material, using a modified Schulze staining method (Schulze-Stöhr technic). He discovered a great many nerve fibers in the choroid plexus and the tela choroidea and divided them into two groups—the vascular nerves and the nerves of the plexus (nervi propii). According to Stöhr, the innervation of the choroid plexus, especially its blood vessels, strongly resembles the innervation of the leptomeninges. There are nerve fibers attached to the blood vessels of all calibers in the choroid plexus as well as in the leptomeninges. Stöhr called these fibers vascular nerves. The nerve fibers not directly participating in the vascular innervation he referred to as nervi propii. Particularly ample is the nerve supply of the tela choroidea of the third and fourth ventricles. In this structure there are tiny fascicles of non-medullated fibers, as well as dense plexuses of very thin fibrils. In the tela choroidea of the third ventricle Stöhr saw thickened, pear-shaped nerve endings. In these terminal bulbs the nerve fibers either form tiny fibrillary networks or end in minute terminal knobs. Stöhr assumed that these two types of nerve terminations have the character of afferent nerves. He described the origin of the nerve fibers of the choroid plexus as follows: The nerve fibers proper of the choroid plexus of the fourth ventricle arise in the nucleus of the tenth nerve, in the pons varolii and in the pedunculi cerebri. Nerve fibers from the brain substance itself enter into the plexus choroideus which overlies the thalamus. The tela choroidea of the third ventricle receives nerve fibers directly from the striae medullares. Stöhr confirmed the opinion of other authors that the sympathetic fibers of the leptomeninges and of the choroid plexus arise from the internal carotid and the vertebral plexus. However, neither Stöhr nor the others demonstrated the origin of the nerves of the choroid plexus by special technics or by experiments.

Junet [3] fixed the plexus choroideus of a mouse *in toto* by the method of Stöhr and identified a perivascular nerve plexus and fascicles of nerve fibers in the stroma of connective tissue. He also described subepithelial nerve plexuses and tiny fibrils which entered the epithelial cells. These fibrils often terminated in little whirls.

Clark [4] studied the innervation of the fourth ventricle. His experimental animals consisted of cat embryos and newborn and young cats, as well as dogs, rats and rabbits. He used Ranson's staining method with pyridine and silver. He established a difference in the innervation of the lateral and that of the medial portion of the choroid plexus. He stated the belief that innervation of the lateral portion resembled the innervation of the cerebral membranes, as described by Stöhr. The

3. Junet, W.: A propos d'un plexus choroïde justa-hypophysaire chez l'Uromastix acanthinurus (Bell), Compt. rend. Soc. de biol. **97**:556 (July 22) 1927.

4. Clark, S. L.: Nerve Endings in the Choroid Plexus of the Fourth Ventricle, J. Comp. Neurol. **47**:1-21 (Dec.) 1928.

nerves of the lateral part of the plexus of the fourth ventricle had a twofold source. Some accompanied the vessels, whereas others originated in the dorsolateral area of the medulla oblongata and formed a fascicle, referred to as the "thirteenth nerve" by Benedikt. The nerve fibers of the medial portion originated in the substance of the medulla oblongata and joined the choroid plexus by way of the taeniae acusticae. The nerves of the plexus choroideus of the fourth ventricle showed well defined terminations, the type of which reminded one of sensory nerve endings.

In his studies on the innervation of the meninges of man at the level of the medulla oblongata, Snessareff concentrated his attention on the tela choroidea. In the tela choroidea of the fourth ventricle both solitary fibers and small fascicles of nonmedullated and medullated nerve fibers are present. Many of the nerve fibers characteristic of the tela choroidea are distinguished by certain peculiarities. They spread out under the epithelium without forming the fascicles or plexuses so characteristic of the meninges. These fibers are nonmedullated, show few varicosities and lack the cells of Schwann. In the choroid plexus of the fourth ventricle, besides vascular nerve fibers, others of the terminal type were discovered by Snessareff, the ramifications of which surrounded the epithelial cells like a network. The author did not agree with Stöhr's division of the nerve fibers into vascular and proper nerves; he suggested, rather, that the former be defined as a nerve plexus of the vascular walls and the latter as an intervascular plexus.

Shapiro [5] did research on the innervation of the choroid plexus of man and various mammals. Fresh material was used, never older than twelve hours. She employed the silver staining methods of Ramón y Cajal, Bielschowsky, Gros-Bielschowsky, Schulze and Stöhr and the old and new methods of Golgi. She drew attention to the great technical difficulties, explained by the impossibility of making frozen sections and by the presence of numerous salts and amyloid and hyaline corpuscles in the tissues. The best results were obtained with the Schulze-Stöhr staining method. Shapiro observed that the choroid plexus was rich in nerve fibers. Fascicles of various calibers contained nonmedullated and medullated nerve fibers. She also saw thick medullated fibers with distinct nodes of Ranvier. The thick bundles of nerve fibers broke up into thinner bundles, from which still thinner bundles were separated, and the latter finally split up into single nerve fibrils. In some of the nerve fibers varicose turgescences and characteristic triangular swellings were present at the sites of ramification. Occasionally, also, dichotomous divisions of the fibers were seen. Single nerve fibers might cross, forming a network of fibers. In the cluster-like portion of the choroid plexus fascicles were absent. The author was able to trace the penetration into

5. Schapiro, B.: Ueber die Innervation des Plexus choroideus, Ztschr. f. d. ges. Neurol. u. Psychiat. **136**:539-546, 1931.

the epithelium of tiny varicose nerve fibrils and their termination between the epithelial cells. There were also thicker medullated nerve fibers in the clusters. Shapiro emphasized that the epithelium of the choroid plexus is scantily supplied with nerve fibers.

MATERIAL AND METHODS

My associates and I studied the innervation of the choroid plexus in dogs and cats. The animals were killed by applying an electric current to the heart. The brain was removed four to six hours after death. Immediately thereafter, or within the next hour, the choroid plexus was extirpated and placed in "A F A" or in neutral solution of formaldehyde U. S. P. ("A F A," used by Lavrentieff, consists of equal parts of 96 per cent alcohol, neutral solution of formaldehyde U. S. P. and a 1 per cent solution of arsinic acid). The hardened choroid plexus was then stained as a whole, without being sectioned. Various silver stains were employed, the Gros-Bielschowsky method yielding the best results. The other silver stains proved unsatisfactory for our material. The stained specimens were affixed to glass plates with albumin-glycerin solution, smoothed out with a glass rod and covered with Canada balsam.

Our specimens showed an ample nerve supply of the vascular plexus of all ventricles. The nerve fibers were scattered in the stroma, around the vessels and subepithelially in the clusters of the choroid plexus. The nerve fibers throughout the connective tissue stroma of the choroid plexus varied slightly in number and distribution from those in its racemose portion. In conformity with other authors, we refer to the nerve fibers surrounding the vessels as vascular nerves. We suggest the name stromal nerves for the nerve fibers scattered through the connective tissue. This term seems to us plainer and more appropriate than the term applied by Stöhr (proper) and that used by Snessareff (intervascular). The nerve fibers run from the vessels of the choroid plexus into the surrounding tissues, whereas from the stroma they take their course to the vessels. This variable course of the nerve fibers makes the classification into two groups appear somewhat schematic and conventional. We noted in the choroid plexus both medullated and nonmedullated fibers, the latter being in the majority. Many fibers showed a rosary-like appearance, indicating their sympathetic origin. In the connective tissue stroma of the choroid plexus fascicles of varying caliber were seen. From the thicker bundles thinner ones branched off, which, in turn, split up into still thinner bundles and, finally, into solitary fibers. The thinnest bundles branched off from the more massive bundles at varying angles. The division of the thin bundles into thinner bundles and into solitary fibers was brought about by dichotomous division, seldom by ramification. At the sites of bifurcation and trifurcation of the nerve fibers the protoplasm became denser and took on a triangular shape (fig. 1 *A* to *F*, inclusive, and *H*; fig. 2 *A* and *B*). The greatest number of massive nerve bundles were observed in the connective tissue stroma of the choroid plexus of the lateral ventricles

Many nerve bundles ran parallel with the fibers of the stroma itself. Some bundles were tortuous, forming knees or other figures, communicated with each other and were plaited together into networks. Such networks might be composed of the fibers of but one bundle. The nerve fibers of the stroma frequently passed over to the vessels, uniting with the vascular nerves. On many slides single nerve fibers were seen, which ended freely in terminal thickenings, resembling little knobs, trowels, spirals or nooses. Such nerve terminations were present in the stroma, as well as around the vessels. The vessels of the choroid plexus of all ventricles were amply supplied with nerve fibers around the adventitia. These fibers were arranged in the longitudinal axis of the vessel, though they often cut athwart the vessel and formed networks and plexuses on its wall. Nerve fibers, of various calibers, were encountered around the vessels. Here and there nerve fibers ran from the vascular walls into the surrounding tissue. Each cluster of the choroid plexus of all the ventricles possessed a subepithelial network of very fine nerve fibers. Either the fibers approached the epithelial cells, ending in knoblike turgescences, or their terminations lay on the very surface of the cells, extending sometimes as far as their nuclei (fig. 1 *G* and *I*). Owing to the technical difficulties of staining, the subepithelial nerve plexuses and the approach of the fibers to the epithelial cells were not visible in all specimens. The tela choroidea of the third and fourth ventricles showed the well known peculiarities of innervation. It was provided with a multiplicity of very fine nerve fibers, running in diverse directions. These fibers, communicating with one another, formed delicate interlacings and networks. There were rosary-like turgescences in many of the nerve fibers. Some solitary fibers ended on the epithelial cells that overlie the tela choroidea. The nerve terminations were analogous in type to the terminations on the epithelial cells of the clusters of the choroid plexus, as previously described.

We did not detect any massive bundles of nerve fibers in the tela choroidea. In none of our preparations were nerve cells observed.

In the experimental part of this work we tried to confirm the assumption of several authors that a known part of the nerve fibers of the choroid plexus originates in the nerve networks of the vessels supplying the choroid plexus. As is well known, the choroid plexuses of the lateral ventricles receive their blood supply from the anterior choroid artery, a branch of the internal carotid artery, and from the posterior choroid artery, a branch of the posterior cerebral artery. For the denervation of the internal carotid artery and its branch, the anterior choroid artery, we removed the superior cervical (sympathetic) ganglion on one side (on the right side). This experiment was performed on cats and dogs. The removal of the superior cervical ganglion was carried out in 19 dogs and cats, but a satisfactory staining of the nerves

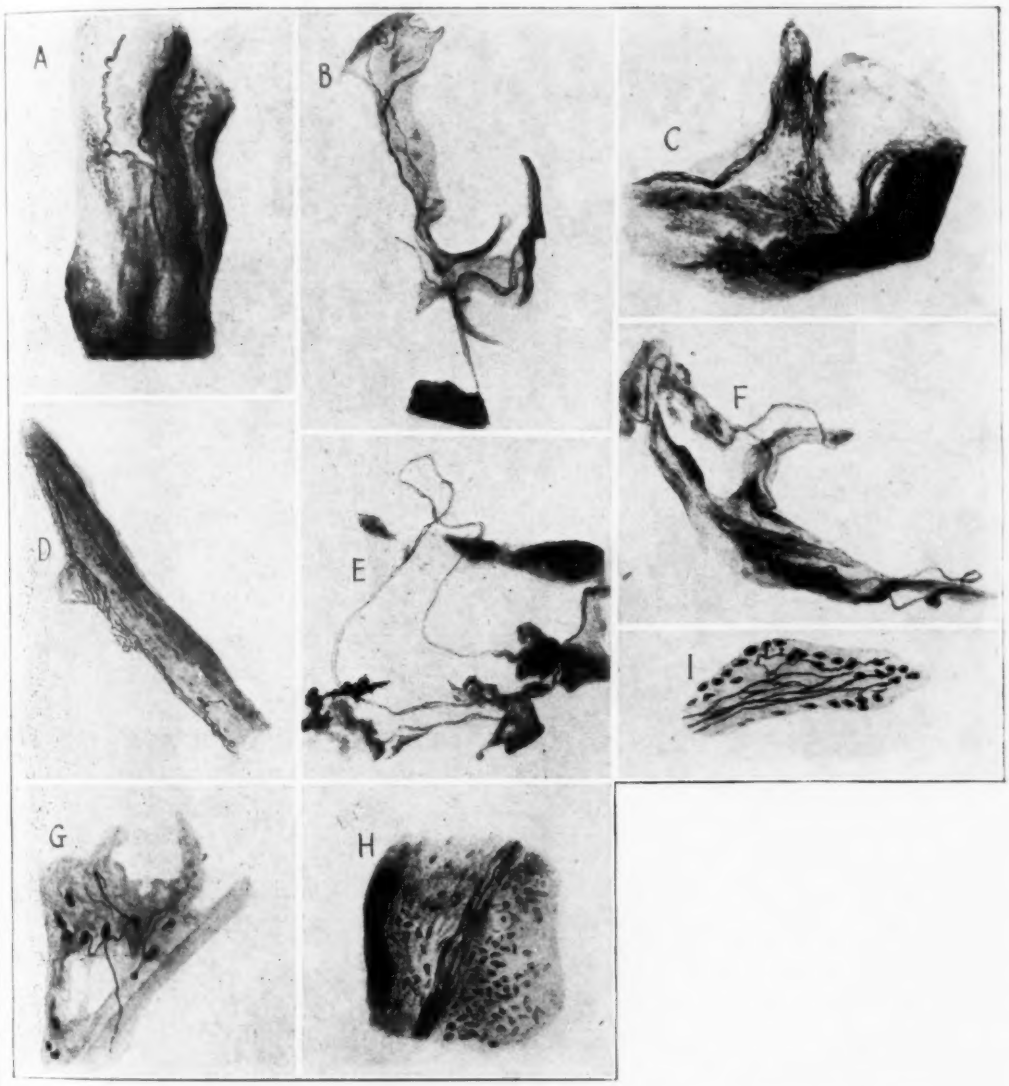

Fig. 1.—*A* (preparation 9; Gros-Bielschowsky stain), nerve fibers in the connective tissue (vascular plexus of the lateral ventricle of a cat). *B* (preparation 9; Gros-Bielschowsky stain), bundles of nerve fibers in the connective tissue (vascular plexus of the lateral ventricle of a cat). One of the bundles passes over into the cluster-like portion. *C* (preparation 9; Gros-Bielschowsky stain), distribution of nerve fibers on the border of connective tissue (vascular plexus of the lateral ventricle of a cat). *D* (preparation 10; Gros-Bielschowsky stain), nerve fibers in a cluster-shaped portion (vascular plexus of the fourth ventricle of a dog). *E* (preparation 7; Gros-Bielschowsky stain), nerve fibers in the connective tissue (vascular plexus in the lateral ventricle of a cat). *F* (preparation 6; Gros-Bielschowsky stain), course and distribution of nerve bundles in the connective tissue (vascular plexus of the lateral ventricle of a dog). *G* (preparation 14; Schulze-Stöhr stain; × 400), termination of nerve fibers on epithelial cells (vascular plexus of the lateral ventricle of a cat). *H* (preparation 1; Gros-Bielschowsky stain; × 400), bundle nerve fibers, spreading along vessels (vascular plexus of the third ventricle of a cat). *I* (specimen 18; Schulze-Stöhr stain; × 400), nerve fibers inside cluster and nerve terminations on epithelial cells (vascular plexus of the lateral ventricle of a cat).

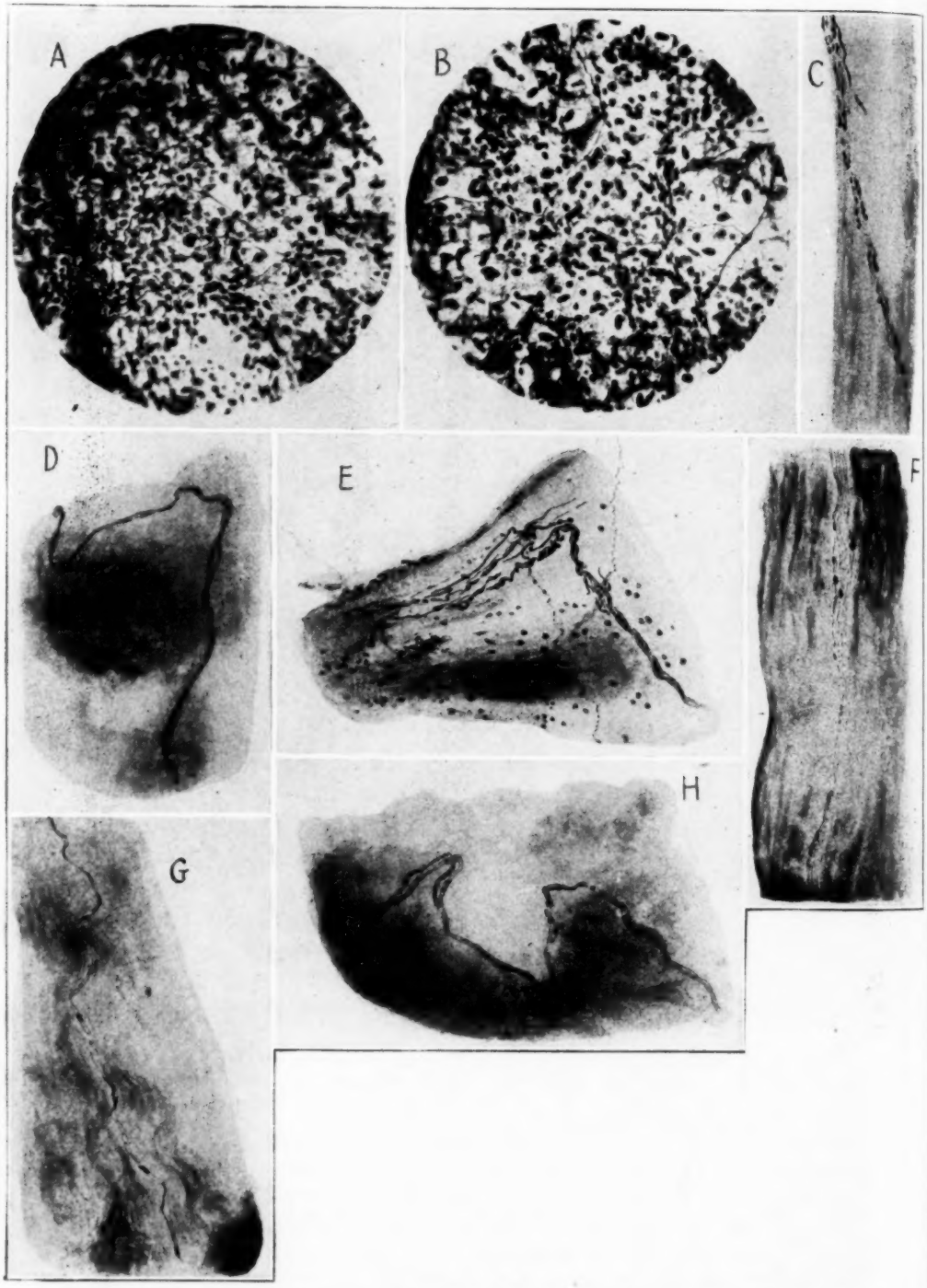

Fig. 2.—*A* (preparation 19; Gros-Bielschowsky stain), thin nerve fibers with their network, dense protoplasm, bifurcations and trifurcations at sites of division of fibers (tela choroidea of the third ventricle of a cat). *B* (preparation 19; Gros-Bielschowsky stain), thin nerve fibers, many of them with a rosary-like appear-

(Legend continued on next page)

of the vascular plexus was obtained in only 13 animals. By the unilateral removal of the sympathetic ganglion we were able to compare the innervation of the choroid plexus of the lateral ventricle on the side of the extirpated ganglion with the innervation of the normal plexus.

The staining of the nerve fibers of the choroid plexus from the right lateral ventricle yielded good results in 9 animals, while the staining of the corresponding structures from the left ventricle turned out well in 8 animals. The nerve fibers of the choroid plexus from the third ventricle stained well in 10 animals. The signs of degeneration of the nerve fibers were argentophilia, fragmentation, complete disintegration and disappearance of the axis-cylinders. We observed them in 7 out of 9 stained vascular plexuses of the right lateral ventricle, i. e., on the side on which the superior cervical ganglion had been extirpated. These changes apply to argentophilia, fragmentation and the breaking up of axis-cylinders into the smallest particles, leaving behind the empty nerve sheaths (fig. 2 *C* to *H*, inclusive). Such changes were seen only in single fibers and in a few fiber bundles. The pathologic nerve fibers lay in the stroma and around the vessels. The main portion of the nerve fibers in the corresponding controls showed normal structures. It is noteworthy that in no slide bearing the choroid plexus of the left lateral ventricle, i. e., the ventricle on the normal side, were degenerations of nerve fibers traceable.

These findings suggest that with the removal of the superior cervical ganglion there develops in the choroid plexus of the homolateral lateral ventricle a degeneration of single nerve fibers and their bundles lying in the stroma of the network and around the vessels, whereas the major portion of the nerve fibers of this plexus remain intact. Evidence of degeneration exists sometimes forty-eight hours after the extirpation of the ganglion. As to the exact time of the appearance of the greatest structural changes, no definite conclusions could be derived from our material.

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ance (turgescences) (tela choroidea of the third ventricle of a cat). *C* (preparation 15; Gros-Bielschowsky stain), coarse disintegration of axis-cylinders into single minute particles (vascular plexus of the right ventricle of cat 8). *D* (preparation 48; Gros-Bielschowsky stain); degeneration of nerve fibers, disappearance of axis-cylinders, empty nerve sheaths (vascular plexus of the third ventricle of cat 28). *E* (preparation 59; Schulze-Stöhr stain), degeneration of nerve fibers, disintegration of axis-cylinders, regrowth and thickening of nerve fibers (vascular plexus of the left ventricle of a dog; in this dog, "Zhuchka," the superior cervical ganglion on the left side had been removed). *F* (preparation 40; Gros-Bielschowsky stain), marked disintegration of nerve fibers and fragmentation (vascular plexus of the third ventricle of cat 17). *G* (preparation 1; Gros-Bielschowsky stain), disintegration of nerve fibers, absence of axis-cylinders, empty sheaths, Schwann cells (vascular plexus of the right ventricle of cat 3). *H* (preparation 1; Gros-Bielschowsky stain), marked disintegration and partial disappearance of axis-cylinders. Here and there are empty sheaths (vascular plexus of the right lateral ventricle of cat 3).

Five out of 10 stained plexuses of the third ventricle showed degeneration of part of the nerve fibers. The histologic changes resembled those seen in the plexus of the right lateral ventricle. Numerically, the changes in the fibers were few. In the specimens showing degenerative changes the majority of nerve fibers had retained their normal appearance. In the choroid plexus of the remaining 5 animals no structural changes of the nerve fibers were noted. This demonstrates that the extirpation of the superior cervical ganglion can produce degeneration of single nerve fibers of the choroid plexus of the third ventricle.

COMMENT

Our experimental observations prove that part of the nerve fibers of the choroid plexus of the lateral ventricle are derived from the network of nerves surrounding the branches of the internal cartoid artery. The main artery supplying the choroid plexus of the lateral ventricle is the anterior choroid artery, a branch of the internal carotid artery, which receives its nerve fibers from the network of the internal carotid artery. The innervation of the internal carotid artery is mainly, though not exclusively, made up of sympathetic fibers from the superior cervical ganglion. The degeneration of part of the nerve fibers belonging to the plexus of the lateral ventricle after the extirpation of the superior cervical ganglion is explained by the fact that these fibers run to the choroid plexus conjointly with the anterior choroid artery; i. e., they are extensions of the plexus fibers of the internal cartoid artery. As previously stated, we noticed degenerative processes in only a few of the nerve fibers, whereas the major portion remained intact. We interpret this in the following way: First, the extirpation of the ganglion does not lead to complete denervation of the internal carotid artery, and, consequently, it cannot cause a complete denervation of its branches, to which the anterior choroid artery belongs. Second, one must take into account that the choroid plexus of the lateral ventricles is supplied with blood also from the posterior choroid artery, which is a branch of the posterior cerebral artery, and that part of the nerve fibers doubtless run to the choroid plexus conjointly with this artery. Third, one may reasonably conjecture that not all nerve fibers of the choroid plexus of the lateral ventricles are derived from nerve networks of blood vessels supplying the choroid plexus. Degeneration of nerve fibers in the choroid plexus of the third ventricle was seen only in half the specimens, indicating that one was not dealing with a constant feature, such as was present in the plexus of the lateral ventricle on the side of extirpation of the ganglion. The choroid plexus of the third ventricle receives its blood supply from the branches of both internal carotid arteries. This special blood supply of the plexus of the third ventricle probably accounts for the inconstant appearance of degeneration of nerve fibers after the

unilateral extirpation of the superior cervical ganglion. With regard to the innervation of the choroid plexus of the third ventricle, it is a logical assumption that not all nerve fibers of this structure come from the nerve networks of the vessels supplying the choroid plexus.

CONCLUSIONS

The results of our experiments with extirpation of the superior cervical ganglion confirm the theory of other investigators, according to which part of the nerve fibers of the choroid plexus originate from the nerve network of the blood vessels supplying the plexus. Our results, further, prove that the origin of certain portions of the nerve fibers belonging to the choroid plexus of the lateral ventricles, and, to a minor degree, of the corresponding structures of the third ventricle, lies in the nerve networks of branches of the internal carotid artery, springing from the superior cervical ganglion. Finally, our observations give evidence that in all probability not all nerve fibers of the choroid plexus originate from the nerve networks of the arteries.

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CLINICOPATHOLOGIC ASPECTS OF PARKINSONIAN STATES

Review of the Literature

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THE DIVERSITY of opinion surrounding (1) the minimal pathologic substrate of the parkinsonian syndrome and (2) the correlation between specific pathologic changes and component parts of the syndrome is well known. A new review of the literature of the clinicopathologic aspects of parkinsonism was accordingly undertaken to determine whether a comprehensive survey of this material would serve to clarify these matters.

In order to make the problem clear, it may be observed that, while a particular series of cases often suggest definite clinicopathologic correlations, these correlations are exceedingly difficult to substantiate when one examines a large number of differently reported series of cases. The following cases briefly illustrate various incompatibilities.

VARIATIONS IN THE PARKINSONIAN STATE WITH ILLUSTRATIVE CASES

Tremor.—Tremor may appear either on the same or on the opposite side of greatest damage of the substantia nigra or may be absent even though this structure is seriously damaged.

CASE 3 (Benda and Cobb [1]).—*History and Examination.*—A man aged 60 entered the hospital with the chief complaint of weakness and tremor of the left hand. About one year prior to admission he first noted tremor of the left hand, which occurred when the hand was at rest. The tremor spread to the elbow. Just before his admission to the hospital weakness developed in the feet, the weakness being more pronounced on the left side. The patient tended to hold his body slightly flexed. The reflexes were reported to be normal. Rigidity was not mentioned in the report.

Microscopic Study.—On the whole, the cells of the basal ganglia and the subthalamic region were well preserved. Demyelination of the globus pallidus was pronounced bilaterally.

The most outstanding change was in the substantia nigra, which showed loss of cells in the lateral area on both sides, the area of the right side being only two-thirds that of the left. The fibers of the substantia nigra showed definite demyelina-

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1. Benda, C. E., and Cobb, S.: On the Pathogenesis of Paralysis Agitans (Parkinson's Disease), Medicine **21**:95, 1942.

tion. There were changes also in the cerebral cortex, in the pons and in the region of the third ventricle.

In this case advanced pathologic alteration of the right substantia nigra was associated with tremor of the left side.

CASE 8 (Benda and Cobb [1]).—*History and Examination.*—The patient had been a backward child, even with special tutoring. He was subject to convulsions during the last years of his life. In a typical attack, he would be found stretched out in bed with head and eyes turned to the right and frothing at the mouth. The right leg jerked spasmodically, and the left arm and leg were stiff. Then followed jerking of the right arm and twitching of the right side of the face. After the attack the tongue appeared to protrude to the left. The grasp of the left hand was weaker than that of the right. The arm reflexes were active and equal on the two sides.

A rhythmic tremor developed, involving especially the left arm and hand and the head, with cogwheel rigidity of the left arm and wrist. Death occurred at the age of 60. The diagnosis was hemiparkinsonism.

Microscopic Study.—Degeneration of cells was widespread in the pallidum, the caudate nucleus and the putamen. The substantia nigra showed patchy degeneration bilaterally, especially on the left side. The inferior olivary nuclei were gliotic. There was fatty degeneration in the nuclei of the tenth, eleventh and twelfth cranial nerves. An angioma was present in the right temporal lobe.

In this case the tremor and rigidity were on the same side of the body as was the more severely involved substantia nigra.

CASE 2 (McAlpin [2]).—*History and Examination.*—A man aged 43 had onset of symptoms in March 1924 with diplopia and insomnia, followed by lethargy. He remained in the hospital four months and during that time began to show signs of parkinsonism. Akinesia and generalized hypertonus were so extreme that he could not walk. There was no tremor. Death occurred on June 11, 1925.

Microscopic Study.—The only significant lesion was a pronounced alteration of the substantia nigra.

In this case the patient was reported to be without tremor, despite the pronounced alteration of the substantia nigra.

Cerebral Cortex.—The cerebral cortext may or may not be the seat of pathologic change.

CASE 4 (Liber and Neustaedter [3]).—*History and Examination.*—A woman aged 24 had the onset of her illness in 1925, characterized by unconsciousness without convulsions. There were generalized muscular pains. She was discharged as recovered in two weeks. Three months later there were tremor of the head and arms and difficulty in walking. She was readmitted to the hospital in May 1926.

Examination revealed tremor of the head and arms, general muscular weakness and slight muscular rigidity. The abdominal reflexes were absent; the plantar

2. McAlpine, D.: The Pathology of the Parkinsonian Syndrome Following Encephalitis Lethargica, with a Note on the Occurrence of Calcification in This Disease, Brain **46**:255, 1923.

3. Liber, A. F., and Neustaedter, M.: Concerning the Pathology of Parkinsonism (Idiopathic, Arteriosclerotic, and Post-Encephalitic), J. Nerv. & Ment. Dis. **86**:267, 1937.

response was normal, but the knee jerk was slightly exaggerated. The pupils were irregular but equal on the two sides; convergence was poor; the light reflex was fair; accommodation was good. A year after admission slight ankle clonus developed on both sides.

Death occurred in February 1934.

Microscopic Study.—Cerebral Cortex: The cortex was normal.

Striatum: The large cells showed distintegration, but the small cells were generally intact.

Globus Pallidus: The ganglion cells were unequal in size. Some appeared normal, but most were small and pyknotic. Many cells were fragmented.

Substantia Nigra: This structure was conspicuously altered. In some regions a few cells were intact.

Cerebellum: Many Purkinje cells were missing. Those present appeared normal. In the dentate and globose nuclei there were islands of atrophic cells.

Substantia Innominata of Reichert: Some cells showed pale cytoplasm. Most of the cells contained an abundance of yellow pigment.

Claustrum: Most of the cells were pyknotic but showed no other change.

Red Nucleus: The large cells revealed a moderate amount of destruction. The small and middle-sized cells had practically disappeared.

Medulla (two levels): This region was essentially normal except for the inferior olivary nucleus, the cells of which were pyknotic and shrunken.

Spinal Cord (first cervical segment): The structure was normal.

This case reveals the diffuse nature of the lesions in postencephalitic parkinsonism. The cortex was reported, however, as appearing within normal limits.

Case 2 (Keschner and Sloane [4]).—*History and Examination.*—A woman aged 24 had a history of encephalitis about one year before her admission to the hospital, while pregnant. Several months after the attack she was unable to use the right upper and lower extremities. This condition was associated with grinding of the teeth and spasmodic contractions of the jaws. She also had severe headaches during this period.

Examination revealed a resting tremor of the right hand and of the head. Muscular rigidity was generalized but was severer on the right side than on the left. There were an extensor plantar response and patellar clonus bilaterally. Convergence was poor; the light reflex was weak, and accommodation was fair. Psychic disturbance revealed itself in lack of interest, untidiness and restlessness. The face was greasy, and saliva drooled from the mouth.

Microscopic Study.—The frontal lobes, thalamus, neostriatum, pons, medulla and cerebellum were normal in appearance. The pallidum, red nucleus and subthalamic nucleus showed only slight perivascular infiltration.

The substantia nigra showed diffuse swelling and destruction of its cells and a conspicuous increase in glia. No neuronophagia was seen. In some sections no remnants of pigment were evident, the cells appearing entirely washed out. The cresyl violet stain showed diminution in the number of cells of the locus caeruleus. Many cells were swollen and exhibited condensation of pigment.

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4. Keschner, M., and Sloane, P.: Encephalitic, Idiopathic and Arteriosclerotic Parkinsonism, Arch. Neurol. & Psychiat. **25**:1011 (May) 1931.

In this case there was little evident pathologic change, but much was left unexplained in the pathologic report. The substantia nigra reflected the greatest damage.

CASE (Weisenburg and Alpers [5]).—*History and Examination.*—A man aged 36 was admitted to the hospital in March and died in April 1925. The onset of illness occurred in November 1924. While at work he began to feel drowsy and continued so for about ten days, when he had to go to bed. Diplopia was also present. He slept all day but poorly at night. In January 1925 he began to have sharp pains in both hands, being severest in the knuckles. The hands became permanently clenched. In February the patient noticed stiffness in the right leg, which soon became completely stiffened. Soon afterward the left leg became stiff. The patient was also troubled with profuse perspiration and ptosis.

There was masking of facial expression, and perspiration was extreme. There was flexor contraction of the arms, hands and fingers. The legs were in rigid extension. The legs and arms could be placed in various positions, which were maintained. The right pupil was larger than the left, but all the cranial nerves were normal. The arm reflexes were barely noticeable because of the rigidity. The patellar and achilles tendon reflexes could be elicited. Neither clonus nor the Babinski sign was elicitable. Active movements were not possible. The Magnus and deKleijn reflexes were not tested.

Gross Pathologic Study.—The brain showed cortical atrophy, especially of the frontal lobes.

Microscopic Study.—The frontal cortex showed a slight disturbance in architecture, especially in the third layer. Satellitosis was evident in the various cortical layers and was widespread. In most of the cells the Nissl substance was absent.

The caudate nucleus for the most part was normal. There was, however, some involvement of the large cells. The small cells of the putamen were normal. Practically all its large cells showed degenerative changes. The cells of the globus pallidus showed slight involvement, but no reduction in number.

In the substantia nigra the cells of the medial group of the zona compacta were greatly reduced and the remainder swollen. Perivascular infiltration was present.

In the red nucleus the pars magnocellularis showed definite cellular changes, varying from satellitosis to complete neuronophagia. The pars parvocellularis showed even severer alterations. The subthalamic nucleus showed no deviation from normal. The medulla was reported as normal, as was the spinal cord.

The authors observed that this case presented a picture considerably like that of the "decerebrate" state. One of the preceding cases (case 4 of Liber and Neustaedter [3]), although unlike Weisenburg and Alpers' case in its clinical aspects, also showed destruction of the red nucleus.

Globus Pallidus.—The pallidum may or may not be the seat of extensive pathologic change.

CASE 3 (Keschner and Sloane [4]).—*History.*—A woman aged 36 was admitted to the hospital in December 1922 and died in June 1927. She had had influenza (?) in 1919. About one year later tremor, bradykinesia and slowness of speech developed.

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5. Weisenburg, T. H., and Alpers, B. J.: Decerebrate Rigidity Following Encephalitis, Arch. Neurol. & Psychiat. **18**:1 (July) 1927.

Examination revealed cogwheel rigidity of all four limbs and a parkinsonian tremor. The plantar responses were normal, but Hoffmann's sign was elicited bilaterally. The abdominal reflexes were active. In July 1923 the rigidity became so severe that she appeared to be in a partial "decerebrate" state. The head was in extreme hyperextension. The pupils reacted poorly to light but reasonably well in accommodation. The patient had attempted suicide before coming to the hospital.

Microscopic Study.—The meninges, cerebral cortex, cornu ammonis, external geniculate bodies, anterior corpora quadrigemina, pons, medulla, hypothalamus, corpus Luysii, cerebellum and red nuclei all appeared normal.

The lateral nucleus of the thalamus showed perivascular infiltration. Both the large and the small cells of the pallidum were darkly stained. The nuclei of the small cells were unusually large. The large cells showed moderately early degenerative changes. A slight increase in glia, without neuronophagia, was present. The putamen was similar to the pallidum. There was no evidence of perivascular infiltration in the striatum.

The caudal portion of the substantia nigra showed great diminution in the number of cells, the remaining cells being swollen and severely degenerated. The glial tissue was greatly increased.

The locus caeruleus was similar to the substantia nigra.

The globus pallidus showed slight état criblé.

The principal lesion in this case was, accordingly, located in the lentiform nucleus and the substantia nigra.

Case (Hohman [6]).—*History.*—A man aged 36, on March 12, 1920, became dizzy, had low grade fever, experienced pain in the elbow and was overtalkative and euphoric. A week later he became cyanotic, listless and seclusive. On March 20 he had generalized tremor, and became restless and sleepless. On March 29, his speech became thick, there was difficulty in swallowing and diplopia developed.

Examination revealed that the reflexes were hyperactive but equal on the two sides; there were a coarse tremor of the extremities and masklike facies. General weakness was present, and he held positions as though cataleptic. His temperature at the time of examination was 100.6 F., and the white blood cell count was 12,600.

There was a progressive increase in rigidity. The temperature continued to range from 99 to 103 F. as long as the patient lived. In the latter part of the illness the deep reflexes were more active on the left side than on the right. Death occurred on June 17, 1921.

Microscopic Study.—Right Putmen and Caudate Nucleus: The number of small and large cells was not diminished. Many of the large cells were practically normal, but some showed severe alteration. The small cells presented a similar picture.

Right Globus Pallidus: The large cells were normal in number and in a much better state of preservation than those in the putamen and the caudate nucleus of that side.

Left Putamen: The large cells were reduced in number but were better preserved than those on the right side. The small cells were also better preserved than those on the right.

Left Globus Pallidus: The cells were normal.

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6. Hohman, L. B.: The Histopathology of Post-Encephalitic Parkinson's Syndrome, Bull. Johns Hopkins Hosp. **36**:403, 1925.

Substantia Nigra (left and right): Whole islands of pigment cells were wiped out. The remaining pigment cells were degenerating.

Subthalamic Body: The structures were normal.

Inferior Olivary Body: The cells were intact.

Nucleus Ambiguus: Alterations were present but were not greater than were to be expected from the fever.

Reticular Substance: The large motor cells were altered.

Dorsal Vagal Nucleus: The cells were affected.

Spinal Cord: The anterior horn cells showed changes attributed to the febrile state.

Precentral Cortex (left): There was damage to the larger pyramidal cells.

The diffuse nature of the lesions associated with postencephalitic parkinsonism is evident in this case, but most of the pathologic alteration was located in the striatum. The precentral cortex was also injured.

Cases such as the preceding ones offer many difficulties to acceptance of the belief that parkinsonism is based on a simple, specific neuropathologic process. It is, perhaps, in Hunt's [7] syndrome of juvenile paralysis agitans that the concept of such specificity reached its highest development. This syndrome usually begins before adolescence and is slowly progressive. As far as could be ascertained, Hunt published only 1 autopsy report. This revealed a selective destruction of the large cells of the lenticular nucleus. A corroborative autopsy was reported by van Bogaert.[8]

One of the difficulties attendant on any attempt to determine just what neuropathologic factors are responsible for parkinsonism is the possibility not only that the disease may require multiple lesions but also that certain lesions of the neuroaxis may prevent its appearance in typical form. Recent neurosurgical experience has suggested that parkinsonism may be abolished or so altered as to be unrecognizable after operation on the frontal lobe. Such cases have appeared in the older literature from time to time.

Garcin and associates [9] gave the following account of a case of left-sided parkinsonian syndrome. The patient, a man aged 45, showed rigidity of the left side with cogwheel phenomena and absence of associated movements on that side and masking of facial expression. The "postural reflexes" were hyperactive. No other abnormal reflexes were found. A very fine tremor of both upper limbs was present. The patient had been subject to intermittent seizures for a number of years; papilledema developed a short while before operation. At oper-

7. Hunt, R.: Progressive Atrophy of the Globus Pallidus, Brain **40**:58, 1917.

8. van Bogaert, L. M.: Contribution clinique et anatomique à l'étude de la paralysie agitante, juvénile primitive (Atrophie progressive du globe pâle de Ramsay Hunt), Rev. neurol. **2**:315, 1930.

9. Garcin, R.; Klein, M. R.; Kipper, M., and Le Bozec: Hémisyndrome parkinsonien gauche par tumeur fronto-calleuse droite disparaissant complètement après ablation de celle-ci (présentation de malade), Rev. neurol. **75**:80, 1943.

Author	Case No.	Cerebral Cortex	Cerebellar Cortex	Dentate Nucleus	Ansa Lenticularis	Inferior Olivary Nucleus	Pallidum	Striatum: Small Cells
Barretto Netto, M.: Arch. brasil. de med. **34**: 107, 1944	2	+	..	..	++	..	+++	..
Liber and Neustaedter [3]	1	—	+	+	..	++++	+++	±
	2	—	+	++++	..	++++	+++	±
	3	—	+	+	..	++++	+++	±
	4	—	+	++	..	++++	+++	±
	5	—	+	+	..	++++	+++	±
	7	—	+	+	..	++++	+++	±
	8	—	+	+	..	+	+++	±
	9	—	+	+	..	++++	+++	±
	10	—	+	+	..	++++	+++	±
	11	—	+	+	..	++++	+++	±
Hunt, J. R.: Arch. Int. Med. **22**: 647 (Nov.) 1918	1	—	—	—	+	—	±	—
	2 §	—	—	—	++	—	++	—
Kesebner and Sloane [4]	1	±	—	—	—	—	±	++
	2	—	—	—	—	—	±	—
	3	—	—	—	—	—	++	+
	4	—	—	—	+	—	++	—
	5	†	..	..	..	..	+	++
	6	—	—	—	—	..	+	±
	7	†	..	..	..	..	++	+
Benda and Cobb [1]	1	++	..	..	..	+++	±	+
	2	++	+	++	++	..	++	+
	3	++	..	..	++	..	..	±
	4	+++	..	..	++	..	++	+
	5	++	..	++	..	..	+++	++
	6	++	..	..	++	—	++	+++
	7	++	..	..	+	+	+	++
	8	+	..	..	++	++	++	++
Hohman [6]	..	+	..	..	..	—	±	+
Hunt [7]	..	—	—	—	+	—	+++	—
McKinley, J. C.: Arch. Neurol. & Psychiat. **9**: 47 (Jan.) 1923	..	—	—	—	+	—	±	±
McAlpine [2]	1 (1923)	—	..	..	—	±	±	+
	2 (1923)	—	—	—	..	—	..	..
McAlpine, D.: Brain **49**: 524, 1926	1 (1926)	—	—	—	—	—	—	—
	2 (1926)	—	—	—	—	..	Focal lesion	—
	3 (1926)	—	—	—	..	—	+	—
	4 (1926)	—	—	—	..	—	+	—
	5 (1926)	—	—	—	..	—	±	—
	6 (1926)	—	—	—	..	..	—	—
	7 (1926)	—	—	—	..	..	±	±
	8 (1926)	—	..	..	..	..	—	—
Bahr, M. A.: J. Nerv. & Ment. Dis. **82**: 514, 1935	1	++	..	+++	+	—	+	±
	2	+	..	—	+	—	+	+
Weisenburg and Alpers [5]	1	++	..	..	..	—	+	—
Davison, C.: A. Research. Nerv. & Ment. Dis., Proc. **21**: 267, 1942	1	+	—	±	+	—	++	..
	2	—	—	—	++	—	+++	..
	3	±	—	+	+	—	++	..
	4	—	.	—	+	—	++	+
	5	—	..	—	+	—	++	—
	6	++	+	+	+	—	++	++
	8	—	..	..	—	—	±	—
	10	±	..	..	+	—	++	++
	11	+	..	..	..	+++	++	+

* In this table, — indicates absence of lesions; ±, questionable structural change; +, slight alteration; ++, moderate ... +++, severe alteration, and ++++, almost total destruction.

The symbols + and — were chosen because they reveal at a glance the relative involvement of different areas. They ... necessarily represent the evaluations of the original worker unless similar symbols were employed. All spaces were filled in ... pletely as the literature allowed.

Reported in the Literature *

Substantia Nigra	Nucleus Basalis	Subthalamic Nucleus	Hypothalamus	Thalamus	Insula	Claustrum	Corpora Quadrigemina Inf.	Corpora Quadrigemina Sup.	Locus Caeruleus	Cornu Ammonis	Corticospinal Fibers	Pons	Medulla	Spinal Cord
++	..	..	..	..	..	..	..	..	..	..	..	..	..	..
++++	+	..	..	..	..	++	..	..	..	..	..	..	—	—
++++	+	..	..	..	..	++	..	..	..	..	..	..	—	—
++++	+	..	..	..	..	++	..	..	..	..	..	..	—	—
++++	+	..	..	..	..	++	..	..	..	..	..	..	—	—
+++±	+	..	..	..	..	++	..	..	..	..	..	..	—	—
—	+	..	..	..	..	++	..	..	..	..	..	..	—	—
++++	+	..	..	..	..	++	..	..	..	..	..	..	—	—
++++	+	..	..	..	..	++	..	..	..	..	..	..	—	—
++++	+	..	..	..	..	++	..	..	..	..	..	..	—	—
++++	—	..	..	..	..	++	..	..	..	..	..	..	—	—
..	..	—	..	—	..	..	..	..	..	..	—	—	—	—
—	+	—	..	—	..	..	..	..	..	..	—	—	—	—
+++	..	+	++	—	..	..	+++	++	+	+	—	—	—	..
++++	..	±	..	—	..	..	..	..	++	..	—	—	—	..
+++	..	—	—	±	..	..	..	—	+++	—	—	—	—	..
++	..	—	..	++	..	..	..	..	+++	—	—	—	—	..
+++	..	+	..	±	..	..	..	..	+++	..	..	..	..	..
..	..	..	..	..	..	..	..	..	++	—	—	—	..	..
++	..	—	—	—	..	..	..	..	..	..	..	..	..	..
++	..	..	..	±	..	..	..	..	..	..	..	..	..	..
+++	..	++	..	..	..	..	..	..	..	..	..	..	..	..
+++	..	±	..	..	..	..	..	..	..	..	—	..	..	..
Not available	..	..	..	..	..	..	..	..	..	..	..	..	..	..
+++	..	..	..	..	..	..	..	..	..	..	..	+	+	+
+++	..	..	..	..	..	..	..	..	..	..	..	—	—	—
+	+	..	..	—	..	..	..	..	..	..	..	..	+	±
++	++	+	..	..	++	++	..	..	..	..	++	..	+	..
+++	..	—	..	..	..	..	..	..	..	..	..	..	+	±
—	++	—	..	—	..	..	..	..	..	..	—	—	—	—
+++	..	..	..	++	..	..	..	..	..	..	±	±	±	±
+++	..	—	..	+	..	..	..	..	±	..	—	±	±	—
±	..	+	+	+	..	..	..	..	..	..	+	—	—	—
+++	..	—	..	—	..	..	..	..	+	..	—	—	—	..
+++	—	—	..	—	..	..	..	..	+++	..	..	±	—	..
+++	—	—	..	—	..	..	..	..	..	..	..	—	—	..
++	—	—	..	..	..	..	..	..	++	..	..	±	—	..
+++	—	—	..	..	..	..	..	..	+++	..	..	±	—	..
+++	—	—	..	—	..	..	..	..	++	..	..	—	—	..
+++	—	—	..	—	..	..	..	..	+	..	..	±	—	..
+++	—	—	..	±	..	..	..	..	..	..	..	..	..	..
+++	..	—	—	—	..	..	..	..	..	..	++	—	—	—
+++	..	..	—	—	..	..	..	..	..	..	++	—	—	—
++	..	—	..	++	..	..	..	..	..	..	—	..	—	—
+++	..	—	—	—	..	..	..	..	—	..	..	..	—	—
+++	..	—	±	—	..	..	..	..	—	..	..	..	..	—
+++	..	++	..	±	..	..	..	..	±	..	..	..	..	—
+++	..	—	—	+	..	..	..	..	++	..	..	..	..	—
+++	..	±	—	—	..	..	..	..	..	..	..	..	..	..
++	..	—	..	++	..	..	..	..	±	..	++	+	+	+
++	..	—	..	..	..	..	..	..	..	..	—	..	..	..
++	..	±	±	—	..	..	..	..	—	..	—	..	..	..
+	..	..	..	..	..	..	..	..	..	..	..	..	..	..

* Only midbrain and basal ganglia studied.
† Juvenile paralysis agitans.

ation, performed after ventriculographic study, a tumor about the size of an orange was removed from the right frontal lobe. The posterior portion of the tumor was slightly anterior to the motor cortex. It extended through the corpus callosum to the opposite side. The tumor filled the frontal horn of the right lateral ventricle. It infiltrated the caudate nucleus and probably the anterior part of the thalamus. After the operation the parkinsonian syndrome cleared completely. Histologically, the tumor was an astroblastoma.

Another condition which has some of the attributes of the parkinsonian syndrome, but which as yet has received no nosologic position, is that described by Hallervorden and Spatz [10] and other neuropathologists. The condition is characterized by progressive muscular rigidity, affecting several members of the same family and occasionally associated with a rhythmic tremor or athetosis. The pathoanatomic change is said to consist in striking pigmentation of the globus pallidus and substantia nigra, the iron-containing pigment being seen in neurons and glial cells and lying free in the tissues. The neurons of the pigmented fields show degenerative changes. However, Helfand [11] stated that in his case there was reduced pigmentation of the zona compacta of the substantia nigra, as well as reduced iron content of the dentate nucleus.

One's understanding of the neuropathology of paralysis agitans is not increased by the presence of some unusual cases in the literature. One such case was reported by Keschner and Sloane. A man aged 53 exhibited a parkinsonian picture, including masklike facies, loss of normal associated movements, flexion of the head, cogwheel phenomena of the left upper extremity, monotonous speech and fine tremor of the head and hands. In addition, there were signs referable to the pyramidal tract in both lower extremities and some ataxia of the left arm. The patient died of agranulocytosis eight months after admission to the hospital. Histologic examination revealed no pathologic changes anywhere in the brain except in the inferior olives. Guillain and associates [12] reported a similar case.

The degree and nature of existing discrepancies are sufficiently apparent from the foregoing presentation to indicate the fruitlessness of a detailed description of all the available material. We have, therefore, prepared a tabulation of the location and degree of the pathologic alteration in the cases reported in the literature.

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10. Hallervorden, J., and Spatz, H.: Eigenartige Erkrankung im extrapyramidalen System mit besonderer Beteiligung des Globus pallidus und der Substantia nigra, Ztschr. f. d. ges. Neurol. u. Psychiat. **79**:254, 1922.

11. Helfand, M.: Status Pigmentatus, J. Nerv. & Ment. Dis. **31**:662, 1935.

12. Guillain, G.; Mathieu, P., and Bertrand, I.: La rigidité d'origine olivaire. Ann. de méd. **25**:460, 1929.

In the 53 cases presented as pathologic studies of parkinsonism there is no unanimity of opinion as to the location of the structural change. However, moderate alterations (2 plus or more) were reported to have been exhibited in the substantia nigra in 44 of the 52 cases in which this structure was available for study, in the pallidum in only 29 of the 51 cases in which it could be studied and in the striatum in only 27 of the 51 cases in which it was available.

Since it is known that the substantia nigra undergoes degeneration when the corpus striatum is injured, it is of importance, in coming to a decision as to whether its pathologic condition is primary or secondary, to observe whether this structure was affected in any cases in which lesions were not exhibited in the corpus striatum. Examination reveals that the corpus striatum was not affected in 2 cases in which pathologic changes occurred in the substantia nigra. In 3 cases there was but doubtful involvement of the corpus striatum, and in 7 cases the pathologic alteration in the latter structure was slight. Approximately 10 per cent of the cases, therefore, suggest that the pathologic process in the substantia nigra is of a primary type. On the other hand, in all 5 cases in which the substantia nigra was reported normal and in the 1 case in which the pathologic alteration was doubtful definite lesions were exhibited in the corpus striatum. This suggests a probable error in the material of over 11 per cent, indicating that it would be unsafe to come to any conclusion as to whether the nigral pathologic process is of primary or secondary nature.

A disquieting feature of the evidence disclosed by the table is the disagreement between the strong internal consistency of the pathologic changes reported by certain authors and the inconsistency when these observations are compared with the pathologic picture reported by others. This has already been discussed. Thus, in all the cases reported by Benda and Cobb alterations were present in the cerebral cortex. In none of Neustaedter's or McAlpine's cases were such lesions present. Nearly all of the cases with a normal substantia nigra were reported by Hunt. In all of Neustaedter's cases, but in only 1 of Hunt's, were there lesions in the cerebellar cortex, the dentate nucleus, the inferior olive and the red nucleus. It is clear that differences of criteria or technic must be responsible for such a situation.

Despite the existence of a number of unusual cases in the literature, in the majority of cases of the parkinsonian state the greater share of the lesions are within the corpus striatum and the substantia nigra. Associated with this picture are minimal diffuse alterations. However, there are sporadic cases in which great destruction appears in almost any suprasegmental nucleus.

A possible explanation of the variations in lesions encountered in studies of the pathology in parkinsonism would be to assume that park-

insonism is not a distinct clincopathologic state but merely an accumulation of superficially similar clinical disorders. At least three clinical varieties of parkinsonism have been distinguished: the idiopathic, the postencephalitic and Hunt's juvenile type, or what may be called heredoparkinsonism. As has already been noted, the pathologic process of the third form was regarded by Hunt to be essentially similar to that present in other forms of the disease. Whether or not there exists a differential pathologic picture for idiopathic paralysis agitans and postencephalitic parkinsonism is as yet unsettled.

Another unsettled problem is the condition of the precentral motor cortex in parkinsonism. There is great need for a thorough clinicopathologic investigation, not merely of this area but of the entire neuraxis, by modern methods of study and according to consistent criteria, applied over a large series of recent cases with autopsy.

It is difficult to tabulate the material of many of the foreign authors. In order that this material may not be neglected, it is necessary to discuss it briefly. Many of these authors (Spatz, in his preface to Klaue's [13] paper; Klaue,[13] Hassler [14] and Trétiakoff [15]) expressed the belief that lesions of the substantia nigra are the most constant and the severest of any associated either with paralysis agitans or with postencephalitic parkinsonism and, moreover, that they are specific for these two diseases. Trétiakoff was among the first to emphasize the apparent constancy of such lesions in paralysis agitans. On the other hand, he not only gave a brief description of eleven other diseases in which alterations of the substantia nigra were noted but also observed that he had never seen a case in which the substantia nigra only was involved. His cases are not reported here, since his interest was limited to the pathology of the substantia nigra and the surrounding midbrain.

Emma [16] studied the substantia nigra in 65 cases with varied causes and without extrapyramidal signs. In 21 of this series, alterations were present in the substantia nigra. The conclusion was reached, accordingly, that such lesions were reactions to nonspecific morbid stimuli.

Klaue based his conclusions on a study of the brains in 32 cases of paralysis agitans and 28 cases of postencephalitic parkinsonism. As controls, he studied the brains of 12 persons who had shown no neurologic or psychic disease and who had died between the ages of 51 and

13. Klaue, R.: Parkinsonsche Krankheit (Paralysis agitans) und postencephalitischer Parkinsonismus, Arch. f. Psychiat. **111**:251, 1940.

14. Hassler, R.: Zur Pathologie der Paralysis agitans und des post-enzephalitischen Parkinsonismus, J. f. Psychol. u. Neurol. **48**:387, 1937.

15. Trétiakoff, C.: Contribution à l'étude de l'anatomo-pathologie du locus niger de Soemmering, Thesis, Paris, no. 293, 1919.

16. Emma, M.: Contributo alla conoscenza della istopatologia della substantia nigra, Riv. di pat. nerv. **36**:483, 1930.

83 years. After this, he examined 10 brains of persons with senile dementia or schizophrenia who had exhibited no clinical signs of extrapyramidal disease.

He reported that, of his controls, some showed that a decrease in bulk of the frontal lobes was due to a disappearance of cortical cells accompanied with some increase in glial elements. The striatum was practically free of disease. Some of the brains had pallidal lesions, which consisted of accumulations of lipid pigment and consequent pigment atrophy, with some disappearance of nerve cells. Glial alterations were also observed. The vessels of the pallidum showed pseudocalcification, of varying intensity. Even very old patients could, however, be free of these changes. The substantia nigra was always normal.

Klaue said that his observations were in complete agreement with those of Gellerstedt [17] in 50 normal cases of old people and by Oseki [18] in 10 cases, adding that the last author stressed the fact that the lesions observed in the basal ganglia of normal aged persons were not less pronounced than those described by Lewy [19] in patients with paralysis agitans.

Klaue gave a complete pathologic report of only 2 cases, which he considered illustrative of the typical pathologic pictures of the two types of disease, paralysis agitans and postencephalitic parkinsonism. His opinion on the pathology of paralysis agitans may be summarized as follows:

In the substantia nigra, all cell groups of the black zone of the zona compacta showed pathologic alterations with complete disappearance of some cell islands. Such changes were more striking in the caudal region of this nucleus. The locus caeruleus showed changes similar to those in the substantia nigra, but of milder degree. Pigmentary atrophy was observed in the inferior olives. The cerebral cortex, basal ganglia, dentate nucleus and cerebellar cortex were all within normal limits.

This picture may be contrasted with the pathologic substrate of postencephalitic parkinsonism as he described it. In this disease, the lesions of the substantia nigra were concentrated in the zona compacta but were more diffuse and complete than in paralysis agitans. The cerebral cortex and basal ganglia were not involved. No definite lesions were noted in the nuclei of the hypothalamus, but the locus caeruleus, again, was observed to be altered like the substantia nigra, but to a milder degree than the zona compacta.

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17. Gellerstedt, N.: Zur Kenntnis der Hirnveränderungen bei der normalen alters-involution, Upsala läkaref. förh. **38**:193, 1933.

18. Oseki, M.: Ueber die Veränderungen des Striatum im normalen Senium, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **26**:339, 1924.

19. Lewy, F. H.: Zur pathologischen Anatomie der Paralysis agitans, Deutsche Ztschr. f. Nervenh. **50**:50, 1913.

Klaue expressed the belief that the pathologic changes of paralysis agitans were not fundamentally different from those of postencephalitic parkinsonism and argued that this supported his belief that two diseases have the same etiologic agent. He was convinced that the lesions of the substantia nigra form the pathologic substrate of both paralysis agitans and postencephalitic parkinsonism. In his foreword to Klaue's paper, Spatz concurred in these views.

In an elaborate study of the organization of the substantia nigra, Hassler [14] said that a somatotopical arrangement of the cell groups of the zona compacta is probable; that is, according to his cytoarchitectural designations, areas Spvl and Spev would appear to be related to the function of the arm. He explained the supposed specificity of the lesions in paralysis agitans and postencephalitic parkinsonism by postulating special pathoclitic properties of the cells of the zona compacta for a noxious agent common to the two conditions. Such pathoclisis, he stated, also existed to a less extent in the cells of the locus caeruleus and the dorsal vagal nucleus.

When one remembers the disproportionality in pathologic methods for demonstrating alterations in large cells as against small cells and in large fibers as compared with small fibers, together with the difficulty in controlling the condition of the autopsy material, one can appreciate the task which confronts the pathologist. If one adds to this the little understood effects of lesions on ascending and descending tracts and nuclei (Hare and Hinsey,[20] Tower,[21] Lassek,[22] Hunt [23] and Davison,[24]) it would not be surprising to find that classic pathology may fail to account for all the morbid processes in the diseases discussed.

CONCLUSIONS

No constant pathologic substrate for parkinsonism may be determined from the cases reported in the literature. The possibility that parkinsonian states are a complex rather than a single clinicopathologic entity might explain such a situation, but the common clinical elements seen among all such cases should be reflected in a common pathologic factor. The most common alteration is that in the substantia nigra, and the most consistent clinical finding is the peculiar tremor. The fact

20. Hare, W. K., and Hinsey, J. C.: Reactions of Dorsal Ganglion Cells to Section of Peripheral and Central Processes, J. Comp. Neurol. **73**:489, 1940.

21. Tower, S. S.: Pyramidal Lesion in the Monkey, Brain **63**:36, 1940.

22. Lassek, A. M.: The Pyramidal Tract (A Study of Retrograde Degeneration in the Monkey), Arch. Neurol. & Psychiat. **48**:561 (Oct.) 1942.

23. Hunt, J. R.: Retrograde Atrophy of Pyramidal Tract, J. Nerv. & Ment. Dis. **31**:504, 1904.

24. Davison, C.: Syndrome of Anterior Spinal Artery of the Medulla, Arch. Neurol. & Psychiat. **37**:91 (Jan.) 1937.

that the substantia nigra is not invariably involved in cases of such tremor not only may represent errors in interpretation but may suggest that the critical focus is in the vicinity of the substantia nigra rather than in this structure itself. The fact that tremor may not exist with lesions in the substantia nigra need not imply that such changes are without significance, since lesions situated elsewhere in the neuraxis may prevent or mask the appearance of such tremor.

Since parkinsonian states so frequently involve multiple lesions, it would be unwise to discard the possibility that more than one lesion is required for their maturation. Certainly, the multiple lesions which commonly exist do alter the clinical aspects of the case. What may be the minimal accessory pathologic changes required to produce the clinical picture one has no means of knowing, since really comprehensive studies on statistically significant, uniformly fresh material have still to be made.

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Case Reports

BENIGN FOCAL AMYOTROPHY

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OF THE great variety of neurologic disorders associated with atrophy of muscle, most fit into well delineated clinical and pathologic syndromes; yet the problem of the etiologic factors in the degeneration of muscle are among the least understood in neurology. Many generalized diseases may produce sharply localized areas of muscular atrophy, raising the question of why one group of muscles should be singled out to become atrophic while an analogous group is spared by a process acting equally on the two. For example, in hyperthyroidism, in which increased or altered thyroid hormone circulates through the entire body, all the muscles of the body may weaken, and perhaps waste somewhat; but in certain cases the tiny extraocular muscles may show degenerative changes far beyond those seen in other muscles. Lead and other metallic poisons, various hydrocarbons, diphtheria toxin and the poliomyelitis virus are but a few of the pathogenic agents which are distributed throughout the body of the host, yet may produce sharply localized disease of a neuromuscular unit. In reviewing the more important theories of the "enigma of myopathic predilection" in the muscular dystrophies, Wilson [1] stated: "It may be that the morbid processes depend on the constitution of individual muscles." There appears to be little reason to doubt that in neurology, as in other fields of medicine, the so-called selectivity of the site of action of a pathogenic agent may in large part be explained by locally diminished resistance to the onslaught of a noxious agent.

In 1902 Gowers,[2] lecturing at the National Hospital for the Paralysed and Epileptic, urged acceptance of the concept of "muscular abiotrophy," postulating that individual muscles degenerate in the course of a diffusely acting pathogenic process because of an inherent predisposition of these muscles to destruction. Thus, whether a localized area of atrophy of muscle results from infection, endocrinopathy or defective metabolism, the specific site of the atrophy might depend on some local weakness or predisposition to atrophy in the presence of the diffusely acting pathogenic agent. Though this concept of "muscular abiotrophy" is a vague and unsatisfactory substitution of philosophy for factual knowledge, no better explanation has been given since.

This principle of greater susceptibility of individual muscles to degeneration is clearly demonstrated in certain lesions of the peripheral nerves. For example, Pollock,[3] working with cases from World War I,

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1. Wilson, S. A. K.: Neurology, London, Edward Arnold & Co., 1940, p. 989.

2. Gowers, W. R.: A Lecture on Myopathy and a Distal Form, Brit. M. J. **2**:89-92, 1902.

3. Pollock, L. J.: Motor Disturbances in Peripheral Nerve Lesions: (*A*) Muscles Involved in Partial Lesions, (*B*) Order of Restored Motion, Arch. Neurol. & Psychiat. **14**:675-684 (Nov.) 1925.

showed that "whether the nerve [is] slightly or severely injured, the muscles most frequently involved in ulnar nerve lesions are the same. The hypothenar group of muscles and the interossei were most frequently affected." Attempts have been made to explain these differences in susceptibility to degeneration in terms of distance from the nerve cell body, relative phylogenetic age of the muscles and various other factors; but, regardless of the exact mechanism, the fact remains that although the entire nerve has been injured, resulting in defective trophic influences on all muscles within the distribution of the nerve, certain of these muscles show a greater tendency to degenerate.

In terms of the concept of a muscle yielding to atrophy because of an inherent susceptibility, a patient studied at an Army general hospital offered an interesting problem for speculation. There rapidly developed, without known cause, atrophy sharply and exclusively limited to the muscles contained in the first interosseous space of the left hand. I believe no similar case has been reported.

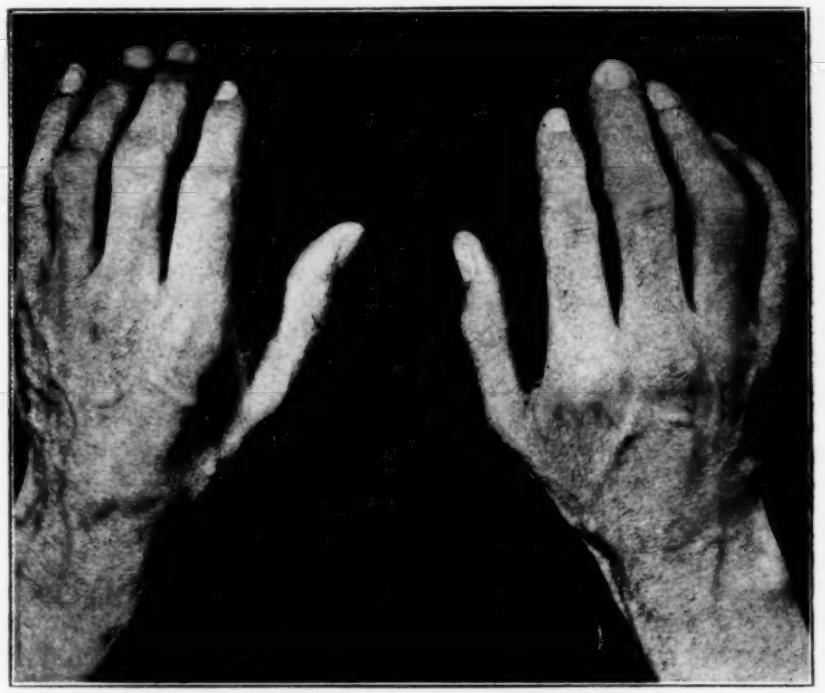
REPORT OF A CASE

History.—A white man aged 29, single, an infantry instructor sergeant who had spent his entire four and one-half years of military service within the continental United States, was admitted to an Army general hospital in December 1945 because of sharply localized atrophy of the small muscles between the thumb and the index finger of the left hand. He had been in excellent health until early in August 1945, when there developed acute nasopharyngitis, with increase in temperature up to 102 F. for a few days, mild malaise, mild diffuse aches and pains and small accumulations of mucus in the pharynx. The review of systems otherwise revealed nothing abnormal; specifically, he had no headaches, nausea, vomiting, stiffness of the neck or back or photophobia. He was hospitalized for nine days, not because he was excessively ill, but in line with Army policy in the control of diseases of the respiratory tract. He was then returned to duty with the diagnosis of "nasopharyngitis, catarrhal, acute, moderate." There appeared to be nothing unusual in the course of this nasopharyngitis. The record of his physical examination at that time stated specifically that his extremities were normal. While the hands might not be carefully inspected in the physical examination of a patient with nasopharyngitis, it is reasonable to believe that if at the time the atrophy in the accompanying photograph (figure) had been present it would not have escaped the attention of the medical officers, nurses and enlisted attendants, not to mention his own attention or that of the soldiers with whom he lived.

Within the few days or few weeks after his discharge from the hospital, he noted that the stability of the left index finger was poor and that the finger slipped when he attempted to use it. This was especially noticeable when he was handling table silver. At the same time, over the course of a few weeks, he noted rapidly progressive wasting of the muscles between the thumb and the index finger of the left hand. At the end of a few weeks there seemed to be no muscle substance remaining in the first interosseous space of that hand. When fasciculations were described to him and shown him in another patient, he expressed certainty that he had never had them in the area of muscular atrophy or elsewhere, and he seemed of a sufficiently observant nature to be reliable on this point.

Shortly after progression of the atrophic process ceased, he became eligible for discharge from the Army because of his adjusted service rating ("discharge

points"). He was, however, persuaded to permit study in the hospital prior to separation. On Dec. 1, 1945 he entered an Army regional hospital, where he was studied for one month. While in that hospital, he participated extensively in reconditioning exercise of his hand, through which he believed he had regained almost normal strength of the left index finger and thumb. He stated that the amount of atrophy had remained unchanged since about October 1945, the atrophic process having run its complete course over a period of one or, at most, two months. On Dec. 30, 1945 he came under my observation, when he was transferred to an Army general hospital with the diagnosis of "other diseases [4] of the nervous system, manifested by weakness of the left index finger and atrophy of muscles between the thumb and the index finger on the dorsal surface of the left hand; cause undetermined."



Atrophy of muscles of the first interosseus space of the left hand.

The patient had had no exposure to heavy metals or to other chemicals. His use of alcohol was very moderate, and he had no abnormalities in his diet or "food fads." He had no history of allergic disorder. Review of the various systems and of his past medical history revealed that he had been healthy throughout life except for the benign illnesses of childhood and occasional colds in adult life. At no time in his life, either civilian or military, had he been employed at a job involving repeated or protracted trauma to the palm of his hand. He had never had a fracture of the elbow or elsewhere in the vicinity of the ulnar nerve. His family history revealed no neuropathic trait.

4. "Other diseases" refers to diseases not listed in any authorized military or civilian medical nomenclature.

Physical and Neurologic Examination.—The patient was well developed, husky and apparently in excellent general physical condition. The only physical abnormality noted was extreme atrophy of the small muscles between the thumb and the index finger of the left hand, involving the first dorsal interosseous muscle and the adductor pollicis. The atrophy of these muscles was sufficient to make the involved area sink in conspicuously (figure). The overlying skin showed no abnormality. There were surprisingly slight weakness of abduction of the left index finger and questionable minimal weakness of adduction of the left thumb. The *signe de journal* was only slightly positive, as evidenced by slight weakness of retention of a piece of paper between the thumb and index finger of the left hand as compared with that of the uninvolved (right) hand when the examiner pulled the piece of paper away. There was no atrophy of muscle elsewhere in the hand or in any other part of the body, and no fasciculations were noted on repeated examination. The rest of the neurologic examination, including specific functional tests of ulnar nerve, revealed no abnormality. The patient was right handed.

Laboratory Data.—Urinalysis and complete blood count gave normal results. The Kahn reaction of the blood was negative. Examination of the stool showed no ova or parasites. Roentgenographic study of the cervical portion of the spine showed no cervical rib or other significant bony abnormality. Spinal puncture revealed a clear fluid, under an initial pressure of 130 mm. of water; examination of the fluid showed 3 lymphocytes per cubic millimeter, a negative Pandy reaction, and 35 mg. of total protein per hundred cubic centimeters. There was no evidence of block in manometric tests. Electrical reaction of degeneration was not present. Faradic and galvanic responses were reported as "the same in the two hands except for slightly less strength in response of the adductor pollicis, the first dorsal interosseous and the first flexor profundus digitorum muscles on galvanic stimulation."

COMMENT

The conspicuous, sharply limited atrophy seen in this case was out of all proportion to the resultant minimal weakness of the involved muscles. There were no fasciculations, no electrical reaction of degeneration, no sensory signs or symptoms, no lesion of the cervical portion of the spine and no abnormalities of the spinal fluid.[5] Observation of the patient could be well controlled in the sense that he was hospitalized and under observation during his nasopharyngitis, as well as later, and was examined by a number of medical officers, who concurred in the physical and neurologic findings. I am fortunate in having been able to secure a follow-up study of the patient for one year, and I can report that there has been no progression in the atrophy described in this paper, nor have any new neurologic symptoms appeared.

The muscles involved in this case, those which lie in the first interosseous space, are supplied by the deep palmar branch of the ulnar nerve. The first dorsal interosseous muscle, which abducts the index finger radiad and flexes the index finger at the metacarpophalangeal joint, makes up the greatest bulk of muscle in the first interosseous space. The adductor pollicis and the medial head of the flexor pollicis brevis (homologue of the first volar interosseous muscle) constitute the remaining bulk of the musculature.

5. Unfortunately, the spinal fluid was not examined until about two months after the atrophy had ceased to progress.

The muscles contained in the first interosseous space waste early and severely in a host of disorders of nerve and spinal cord, including ulnar neuropathy, amyotrophic lateral sclerosis and Aran-Duchenne muscular atrophy, but none of these conditions causes the sharply delimited, severe atrophy seen in this case, with little impairment of function, absence of fibrillations, normal electrical reactions, rapid progression of the atrophy during a few weeks, and then complete cessation of the process. A review of the available literature has disclosed no similar case.

The rapidity of development and limitation of the atrophy suggested first a neuropathic process, perhaps inflammatory, perhaps traumatic, limited to the distal portion of the ulnar nerve, the deep palmar branch. In 1908 Ramsay Hunt [6] described the syndrome of "occupation neuritis of the deep palmar branch of the ulnar nerve." He emphasized the absence of the usual sensory signs and symptoms of neuritis because the deep palmar branch lacks a sensory component. His criteria for this neuritis were, first, atrophic paralysis of all the intrinsic muscles of the hand innervated by the ulnar nerve; second, electrical reaction of degeneration, and, third, absence of objective sensory disturbance in the distribution of the ulnar nerve. He expressed the belief that the "neuritis" resulted from compression of the deep palmar branch as it passes between the small muscles of the hypothenar eminence, as a result of a continued (occupational) pressure on this region of the palm. Subsequently, a number of cases of this syndrome have been reported by Harris [7] and others. No case of "neuritis" of the deep palmar branch of the ulnar nerve showed the sharply limited atrophy present in the case reported here. Moreover, the absence of an electrical reaction of degeneration in the presence of severe atrophy argues, though not incontrovertibly, against a neuritic origin in the present case.

Discrete lesions of constituents of the brachial plexus have caused limited amyotrophies. Without any attempt at a review of the literature, one may point to Wilson's [8] description, in 1913, of atrophy sharply localized to the region of the opponens pollicis and abductor pollicis muscles in cases of cervical rib. Photographs in such cases may also be found in his textbook,[9] as well as in the 1913 report.[8] In 1908 Thompson [10] described "familial atrophy of the hand muscles." Thompson's cases were of interest in that 7 members of a family of 64 persons (five generations) exhibited atrophy sharply localized to the outer (radial) half of the thenar eminence. Roentgenograms of their spines showed the presence of cervical rib, a familial characteristic. Thompson

6. Hunt, J. R.: Occupation Neuritis of the Deep Palmar Branch of the Ulnar Nerve, J. Nerv. & Ment. Dis. **35**:673-689, 1908.

7. Harris, W.: Occupational Pressure Neuritis of the Deep Palmar Branch of the Ulnar Nerve, Brit. M. J. **1**:98, 1929.

8. Wilson, S. A. K.: Some Points in the Symptomatology of Cervical Rib, with Especial Reference to Muscular Wasting, Proc. Roy. Soc. Med. **6**:133-141, 1913.

9. Wilson,[1] pp. 1406-1416.

10. Thompson, T.: Familial Atrophy of the Hand Muscles, Brain **31**:286-300, 1908.

argued that the cervical rib was not the cause of the atrophy; but, as previously mentioned, later workers have shown that cervical rib is capable of causing atrophy as sharply defined as that found in Thompson's cases. In terms of the present case, this is of interest in demonstrating, first, that a lesion of components of the brachial plexus may cause sharply defined atrophy in the hand and, second, that, although the compressed elements of the plexus must have innervated more than the abductor pollicis and opponens pollicis, these muscles were for some reason less able to withstand the process leading to atrophy. In the case reported here there was no cervical rib nor other apparent bony abnormality to account for compression of cervical rootlets or of components of the brachial plexus, but a less apparent lesion might conceivably have existed.

"Distant wasting of the first dorsal interosseous muscle" associated with diminution of epicritic sensibility over the ulnar border of the hand was described by Buzzard [11] as a late sequel of fracture of the external condyle of the humerus seven years previously (rudimentary cervical ribs were also present). Unfortunately, no picture was furnished, and the description did not clearly indicate whether the atrophy was entirely localized to the first dorsal interosseous muscle. The possibility of this "tardy paralysis of the ulnar nerve," first described by Panas in 1878, named by Ramsay Hunt in 1916 and elucidated by a number of investigators,[12] could be ruled out in my case by careful inquiry into the history and by absence of valgus deformity at the elbow.[13]

In 1939 Wartenberg,[14] under the title of "Partial Thenar Atrophy," reported 7 cases with certain points of similarity to the present case. As described by Wartenberg, this consisted of "a peculiar and distinct picture that I have not observed in any other neurologic disease. The cardinal sign in all cases was a partial, sometimes sharply defined, atrophy along the radial, outer, side of the thenar eminence." There was no cervical rib or other bony abnormality. Although 5 of his 7 patients noted paresthesias, there were "no appreciable sensory changes in the hands, fingers or elsewhere." There were no fibrillations. After commenting on the difficulties of electrical examination of the small muscles, Wartenberg noted that in some cases the muscles affected seemed not to react at all, in some cases there was complete reaction of degeneration and in no case was a movement of opposition of the thumb elicited by electrical stimulation. His final comment is of great theoretic interest:

> . . . I prefer not to speak of neuritis and wish to lay more stress on the fundamental importance of the inherent abiotrophy of the two muscles of the hand that

11. Buzzard, E. F.: Some Varieties of Traumatic and Toxic Ulnar Neuritis, Lancet **1**:317-319, 1922.

12. Shelden, W. D.: Tardy Paralysis of the Ulnar Nerve, M. Clin. North America **5**:499-509, 1921.

13. Miller, E. M.: Late Ulnar Nerve Palsy, Surg., Gynec. & Obst. **38**:37-46, 1924.

14. Wartenberg, R.: Partial Thenar Atrophy, Arch. Neurol. & Psychiat. **42**:373-394 (Sept.) 1939.

are involved. Though the partial thenar atrophy may be precipitated by external causes, this constitutional abiotrophy is the primary factor and by itself can produce a pathologic condition of the hands.

In the present case the atrophy was as sharply delimited as in Wartenberg's, but in a different site. In this case, as in Wartenberg's, there was "predominance of the atrophy over the paralysis, whereas in a neuritic disorder one would expect the opposite to occur." One wonders whether his cases, as well as mine, might be included in a concept of a limited area of congenitally inferior muscle, predisposed to degenerate spontaneously or by reason of increased susceptibility to a generally acting pathogenic influence, such as neuritis, compression of the nerve or trauma. The term "benign focal amyotrophy" is suggested as being descriptive, but noncommital regarding site of atrophy or individual precipitating cause.

In 1940 Romano and Michael [15] described 3 cases of partial thenar atrophy, explaining their first case by brachial neuritis, the second by direct trauma to the nerve and the third by the assumption of "involvement of selective fibers of the median nerve," although the exact cause was not apparent. These explanations are in no way contrary to the concept that the inherent weakness of the two muscles involved predisposed them to atrophy, while other muscles innervated by the median nerve were able to withstand the pathologic process.

The preservation of normal electrical reactions in the case reported here, contrary to what is found in cases of neuritis, is curiously similar to what is observed with progressive muscular dystrophy. As Wilson commented [16] in cases of progressive muscular dystrophy "stimulation with either faradic or galvanic current will continue to excite myoplasm so long as sufficient is left to respond." It may be that in either condition an inherent defect of muscle predisposes to degeneration of the affected muscles without interfering with the neuromuscular relation. From a highly theoretic point of view one may speculate on the possibility that some of the focal amyotrophies are formes frustes of the progressive muscular dystrophies.

One may also speculate on the relation between the patient's nasopharyngitis in the present case and his subsequent atrophy of the interosseous muscle. There is the reasonable objection that every neurologic syndrome has been preceded by an incidental "cold." In this connection, Barnes's [17] "toxic degeneration of the lower neurones simulating peripheral neuritis" is often cited, but the absence at that time of modern aids to diagnosis, including spinal puncture, and his lack of histologic material led to misinterpretations drawn from a variety of cases, which appear to have included instances of neuritis and infectious neuronitis.

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15. Romano, J., and Michael, M.: Partial Thenar Atrophy, Arch. Neurol. & Psychiat. **44**:1224-1229 (Dec.) 1940.

16. Wilson,[1] p. 977.

17. Barnes, S.: Toxic Degeneration of the Lower Neurones Simulating Peripheral Neuritis, Brain **25**:479-500, 1902.

SUMMARY

A case with rapidly progressive atrophy sharply and entirely limited to the muscles contained in the first interosseous space is reported. During a period of observation of one year, there has been no progression of the atrophy, and no new neurologic signs or symptoms have appeared. It is believed that no similar case has been reported. Attention is called to certain similarities of this disorder to the syndrome described by Wartenberg under the title of partial thenar atrophy. The name "benign focal amyotrophy" is suggested as descriptive of such an atrophy, but as noncommital regarding the site of atrophy or individual precipitating cause. The concept that focal atrophies may be explained by an inherent inability of certain muscles to withstand the noxious influence of a process which acts on many or all muscles, yet produces atrophy of only a few, is discussed.

Hillside Drive.

News and Comment

RESOLUTION ADOPTED BY THE GROUP FOR THE ADVANCEMENT OF PSYCHIATRY AT MINNEAPOLIS, JULY 2, 1947

Because of recent newspaper and magazine articles which claim that a conflict exists between psychiatry and religion, and because of the resulting confusion of and the harm done to patients and their families, the membership of the Group for the Advancement of Psychiatry, meeting in Minneapolis, believe it is highly desirable to make the following statement:

"For centuries, religion and medicine have been closely related. Psychiatry, as a branch of medicine, has been so closely related to religion that at times the two were almost inseparable. As science has developed, however, medicine and religion have assumed distinctive roles in society, but they continue to share the common aim of human betterment. This also holds true for that method of psychiatry known as psychoanalysis.

"We, as members of the Group for the Advancement of Psychiatry, believe in the dignity and the integrity of the individual. We believe that a major goal of treatment is the progressive attainment of social responsibility. We recognize as of crucial significance the influence of the home on the individual and the importance of ethical training in the home. We also recognize the important role religion can play in bringing about an improved emotional and moral state.

"The methods of psychiatry aim to help patients achieve health in their emotional lives so that they may live in harmony with society and with its standards. We believe that there is no conflict between psychiatry and religion. In the practice of his profession the competent psychiatrist will, therefore, always be guided by this belief."

FACT SHEET

The Group for the Advancement of Psychiatry was organized in May 1946 in Chicago by a number of members of the American Psychiatric Association in an effort to accelerate psychiatric progress by mutual study and discussion of outstanding problems, clarification of concepts and determination of psychiatric needs and concrete steps required to meet those needs. The group now has 126 members from the United States and Canada, all of whom are also members of the American Psychiatric Association. Dr. William C. Menninger, of Topeka, Kan., is its chairman, and Dr. Henry Brosin, of Chicago, its secretary. Activities of the group are financed in part by a grant from the Commonwealth Fund.

The first formal meeting of the group was held Nov. 4 to 6, 1946, in Rye, N. Y., where the main subject of study and discussion was the problem of psychiatry in medical education. The second formal meeting, held at Minneapolis, June 30 to July 2, 1947, was devoted principally to the subject of state psychiatric hospitals.

The Group for the Advancement of Psychiatry comprises fifteen committees, covering medical education, research, preventive psychiatry, therapy, public education, social work, cooperation with federal agencies, cooperation with lay groups, state hospitals, racial and social problems, clinical psychology, industrial psychiatry, forensic psychiatry, international relations and child psychiatry. More than twenty experts in other fields have been invited to serve as consultants.

From time to time, the Group for the Advancement of Psychiatry has adopted reports and resolutions on some of the subjects studied by its committees. A number of these reports will be published in the near future in several professional journals.

AWARD OF FEDERAL GRANTS FOR RESEARCH IN MENTAL HEALTH, UNITED STATES PUBLIC HEALTH SERVICE

Award of the first federal grants for research in mental health under the new National Mental Health Act has been announced by Dr. Thomas Parran, Surgeon General, United States Public Health Service, Federal Security Agency, Washington 25, D. C.

The mental health program, authorized by Congress in 1946, received its first appropriations, totaling $7,500,000, on July 8, 1947. In addition to paying the cost of mental health activities within the Public Health Service, this is to finance a threefold program of research on mental illness, development of local mental health facilities and training of mental health personnel.

Grants announced today go to institutions and individuals to support research projects in fields bearing on the problems of mental illness. The grants were recommended by the National Mental Health Advisory Council, a body of experts in the mental health field, and were approved by the Surgeon General.

Twenty-five research grants have been awarded to the following institutions and individuals:

Indiana University, Bloomington, Ind.; director of project: Dr. W. N. Kellogg, professor of psychology

University of Kansas, Lawrence, Kan.; director of project: Dr. Roger C. Barker, professor of genetic psychology

Dr. Anne Roe, 23-03 44th Drive, Long Island City 1, N. Y.

State University of Iowa, Iowa City, Iowa; director of project: Dr. J. S. Gottlieb, associate professor of psychiatry

Northwestern University Medical School, Chicago; director of project: Dr. Jules H. Masserman, assistant professor, Nervous and Mental Disease

Chicago Institute for Psychoanalysis, Chicago; directors of project: Dr. Franz Alexander, director of institute and Dr. Thomas M. French, associate director of institute (three projects)

The Menninger Foundation, Topeka, Kan.; directors of project: Dr. Eunice M. Leitch, assistant psychiatrist, Menninger Clinic, and Dr. Sibylle K. Escalona, assistant director, Division of Psychology, Menninger Clinic

The Menninger Foundation, Topeka, Kan.; directors of project: Dr. Margaret Brenman, director of division of psychology, Menninger Clinic, and Dr. Merton Gill, assistant director of department of research, Menninger Foundation

Jefferson Medical College, Philadelphia; director of project: Dr. Francis M. Forster, assistant professor of neurology

The James Jackson Putnam Children's Center, Roxbury, Mass.; directors of project: Dr. Marian C. Putnam and Mrs. Beata Rank

Cornell University, Ithaca, N. Y.; directors of project: Dr. Howard S. Liddell, professor of psychology, and Dr. Clive M. McCay, professor of nutrition

University of Pittsburgh, Pittsburgh; director of project: Dr. Wayne Dennis, professor of psychology, and head of department of psychology

Dr. Leopold Bellak, associate in psychiatry, New York Medical College; assistant psychiatrist, Flower and Fifth Avenue Hospitals, New York

Washington School of Psychiatry, Washington, D. C.; director of project: Dr. Alfred H. Stanton, research associate

Marriage Council of Philadelphia, Philadelphia; directors of project: Mrs. Emily Hartshorne Mudd, director of marriage council; Dr. Malcolm G. Preston, research consultant, and Dr. William L. Peltz, psychiatric consultant

New York State Psychiatric Institute, New York; director of project: Dr. Zygmunt A. Piotrowski, associate in psychiatry

Caroline Zachry Institute of Human Development, Inc., New York; director of project: Dr. Lawrence K. Frank, director of Caroline Zachry Institute

Michael Reese Hospital, Chicago 16; director of project: Dr. Samuel J. Beck, head of psychology laboratory (two projects)

Michael Reese Hospital, Chicago; director of project: Dr. Roy R. Grinker, director, Institute for Psychosomatic and Psychiatric Research and Training

Massachusetts General Hospital, Boston; directors of project: Dr. Allan M. Butler, chief of the children's medical service, and Dr. Stanley Cobb, chief of the psychiatric service

The May Institute for Medical Research of the Jewish Hospital, Cincinnati; director of project: Dr. I. Arthur Mirsky, director, The May Institute for Medical Research; associate professor of Experimental Medicine in Medicine; associate professor of Experimental Medicine in Psychiatry (two projects)

GRADUATE FELLOWSHIP AWARDS IN HEALTH EDUCATION, UNITED STATES PUBLIC HEALTH SERVICE

Twenty-five men and women in fifteen states, the District of Columbia and Alaska have been offered graduate fellowships in health education, financed by the National Foundation for Infantile Paralysis, March of Dimes Funds, as

announced by Dr. Thomas Parran, Surgeon General, United States Public Health Service, Federal Security Agency.

In addition to nine months of academic study at an accredited school of public health, starting September 1947, each fellow will have three months of field training in a health department under supervision of a public health educator. Of the 21 persons who have accepted the award, 17 will receive the degree of Master of Public Health, and 4 will receive the degree of Master of Science in Public Health, after satisfactory classroom work and field training.

The award winners, 4 of whom are veterans, were chosen from more than 340 candidates who submitted applications to the Committee on Training of Public Health Personnel of the United States Public Health Service.

The membership of the Health Education Fellowship Awards Committee is as follows: Dr. C. L. Williams Sr., United States Public Health Service, chairman; Dr. Ben W. Miller, American Association for Health, Physical Education and Recreation; Dr. Frank Stafford, United States Office of Education, Federal Security Agency; Dr. A. L. Van Horn, Children's Bureau, Federal Security Agency; Dr. G. M. Wheatley, American Public Health Association, and Miss Catherine Worthingham, National Foundation for Infantile Paralysis.

This year's winners make a total of 83 persons since 1944 who have been granted fellowships from the National Foundation for Infantile Paralysis for graduate study in the field of health education.

Persons who have accepted fellowships for 1947-1948 and the universities they will attend are:

University of California: Ferne R. Fehlman, Mount Morrison, Colo.; Alston H. Haggerty, Berkeley, Calif.; Rita M. Flick, Lewistown, Pa.; Margaret M. Warner, Oconto, Wis.
Columbia University: Anna Obert, Downey, Ill.; Rhoda Woronoff, Washington, D. C.
University of Michigan: Alice Beardslee, Richmond, Va.; George V. Leadbetter, Juneau, Alaska; Howard J. Stroud, Grand Rapids, Mich.; Greta K. Yager, Liberty, N. Y.
University of Minnesota: Ann Switzer, Forest Glen Section, Washington, D. C.
University of North Carolina: Ruth L. Coile, Pinehurst, Ga.; Margaret M. Ervin, Florence, S. C.; Eva V. Higdon, West Asheville, N. C.; Maryrose Johnson, New York; William R. Manning, Logan, Utah.
North Carolina State College: Ida B. Gadsden, Savannah, Ga.; Thomas E. Roberson, Laurel, Miss.
Yale University: Marjory Buntyn, Savannah, Ga.; Lena M. DiCicco, West Roxbury, Mass.; Beatrice A. Hruska, Helena, Mont.

APPOINTMENTS TO NATIONAL ADVISORY MENTAL HEALTH COUNCIL

Dr. Alan Gregg, director, the medical sciences, Rockefeller Foundation, New York, and Dr. Karl M. Bowman, Langley Porter Clinic, San Francisco, have been appointed as members of the National Advisory Mental Health Council of the United States Public Health Service, succeeding Dr. Frank F. Tallman, commissioner of mental hygiene, department of public welfare, Columbus, Ohio, and Dr. George S. Stevenson, medical director, National Committee for Mental Hygiene, New York, whose terms expired.

Dr. Tallman and Dr. Stevenson were appointed as consultants in mental health to United States Public Health Service on July 1, on expiration of their terms on the National Advisory Mental Health Council.

ABSTRACTERS FOR FOREIGN JOURNALS WANTED

Abstracters for French, German and Italian neurologic journals are wanted. The only compensation provided is a subscription to the periodical to be abstracted and to the periodical for which the abstracts are prepared. Please communicate with Dr. Bernard J. Alpers, 111 North 49th Street, Philadelphia 39.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

THE IN VIVO INACTIVATION BY CYANIDE OF BRAIN CYTOCHROME OXIDASE AND ITS EFFECT ON GLYCOLYSIS AND ON THE HIGH ENERGY PHOSPHORUS COMPOUNDS IN BRAIN. H. G. ALBAUM, J. TEPPERMAN and O. BODANSKY, J. Biol. Chem. **164**:45, 1946.

The investigations of Keilin and of Stotz have shown that the cyanide ion combines in vitro with cytochrome oxidase and thereby interferes with the utilization of molecular oxygen by the tissue oxidation-reduction systems. It has also been demonstrated that the utilization of molecular oxygen is coupled with phosphorylation reactions, and Lipmann has emphasized the role of aerobic metabolism in the resynthesis of high energy phosphorus compounds. In the intact animal, the resynthesis of high energy phosphorus compounds is coupled with oxidative processes. The present experiments were undertaken, first, to determine whether brain tissue from cyanide-poisoned rats showed a diminution in cytochrome oxidase activity and, second, to study in some detail the distribution of glycogen, lactic acid and the phosphorylated intermediate compounds in such tissue, particularly with reference to the distribution pattern of high energy phosphorus compounds. Rats given intraperitoneal injections of 5 mg. of sodium cyanide per kilogram of body weight showed approximately a 50 per cent decrease in cytochrome oxidase activity in the brain. The brains of these cyanide-poisoned rats showed significant decreases in the concentrations of glycogen, phosphocreatine and adenosine triphosphate and significant increases in the concentrations of inorganic phosphate, lactic acid, hexose diphosphate, phosphoglycerate and phosphopyruvate. These results indicate that anoxia in tissue induced by inactivation of cytochrome oxidase results in a shift from aerobic to anaerobic metabolism and a depletion of high energy phosphorus compounds.

PAGE, Cleveland.

GENERALIZED ATONIA AND PROFOUND DYSREFLEXIA FOLLOWING TRANSECTION OF THE BRAIN STEM THROUGH THE CEPHALIC PONS. ALLEN D. KELLER, J. Neurophysiol. **8**:275 (Sept.) 1945.

By means of blunt traction, Keller transected the brain stem of dogs at various levels of the midbrain and pons. The dogs were studied by gross clinical inspection for several weeks after operation. An important feature of the operative technic was the maintained integrity of the cerebral circulation. Transections of the upper portion of the pons invariably produced generalized and enduring muscular atonia. Profound dysreflexia occurred after transection of the brain stem at any level of the pons or midbrain. Dysreflexia was more profound in transections of the upper part of the pons. The degree and distribution of the dysreflexia varied somewhat with the level of transection. Spontaneous extensor rigidity did not routinely follow transections of the midbrain, nor was there increased resistance to passive manipulation of muscles. The reflex standing stance was not exaggerated. In low midbrain preparations righting reflexes were impaired.

FORSTER, Philadelphia.

ELECTRICAL ACTIVITY OF THE THALAMUS AND BASAL GANGLIA IN DECORTICATE CATS. R. S. MORRISON and D. L. BASSETT, J. Neurophysiol. **8**:309 (Jan.) 1945.

Morrison and Bassett studied the electrical activity of the thalamus and basal ganglia of cats following decortication. For as long as three days typical bursts of 8 to 12 per second spikes were recorded. In 1 animal bilateral decortication, transection of the midbrain and section of both optic nerves failed to prevent the appearance of the bursts. In cats which had been decorticate from twenty-one days to one year, normal bursts did not appear, but bursts of atypical, low voltage activity occurred in restricted areas. Morrison and Bassett conclude that the spiking activity recorded from the thalamus does not depend in a functional sense on the presence of the neocortex, since they occur in the absence of a high proportion of normal thalamopetal impulses. The ultimate reduction in spiking activity recorded from the thalamus of decorticate preparations is probably due to the disintegration of elements of the thalamus dependent on the cortex for their anatomic integrity.

FORSTER, Philadelphia.

THE ELECTRICAL ACTIVITY OF VOLUNTARY MUSCLE IN MAN UNDER NORMAL AND PATHOLOGICAL CONDITIONS. G. WEDDLE, B. FEINSTEIN and R. E. PATTLE, Brain **67**:178, 1944.

Weddle, Feinstein and Pattle obtained electromyographic records from normal subjects and from patients with various neuromuscular disorders. Studies on normal muscle indicated that no electrical activity can be recorded from completely relaxed muscle. With concentric needle electrodes action potentials of motor units can be recorded. These vary from 100 microvolts to 1 millivolt in amplitude and from five to ten milliseconds in duration. Action potentials of motor units are evoked by contraction and also by the mechanical stimulation incidental to insertion of the needle electrode. Concentric needle electrodes have strong directional properties. The recordable impulse from the action potential of the motor unit can be recorded in a range of 1 to 2 cm. This is considerably less than the theoretic distance at which this impulse should be recordable. The discrepancy is probably due to the directional properties of the electrode. No electrical activity can be recorded from a muscle whose nerve supply has been blocked by a local anesthetic. No simple relation is present between the activity of the motor unit and the degree of muscle tone. The factors concerned in the lack of correlation include (1) the intravascular and extravascular fluid within the muscle sheath; (2) rheologic properties of the muscle; (3) motor unit activity within the muscle with the nervous system intact, and (4) motor unit activity within the muscle with the nervous system damaged or destroyed. These factors are further subdivided.

Weddle, Feinstein and Pattle found in denervated muscle repetitive action potentials when the muscles were at approximately blood temperature. Fibrillary action potentials were of two types—potentials due to mechanical insertion of the needle electrode and rhythmically repeating potentials, presumably due to chemical stimulation. Fibrillations appear after denervation after a longer interval in man than in animals, and the interval depends on the muscle denervated. Thus, fibrillations occur from the tenth to the twelfth day in the sacrospinalis muscle and from the sixteenth to the eighteenth day in limb muscles. Eighteen years after denervation fibrillation potentials were obtained. In partially denervated muscles fibrillations can be obtained, the degree of difficulty in obtaining these potentials depending on the number of denervated motor units. In certain cases in which the lesion is presumed to be the result of axonal interruption fibrillation action potentials cannot be elicited. This may occur when the disease process involves the muscle fibers, the muscle fibers have undergone morphologic changes or the interruption of the axon has not occurred but, instead, the process is one of reversible ischemic block. Cooling denervated muscle decreases the number of fibrillations, whereas warming the muscle increases the activity. Administration of neostigmine increases

the fibrillations. No correlation existed between the number and frequency of fibrillations and the degree or rapidity of muscular atrophy. The application of adequate physical therapy to denervated muscle results in maintaining vigorous fibrillation, whereas untreated denervated muscle fibrillates feebly. In cases of ischemic block which is reversible insertion potentials can always be elicited, and a few repetitive motor unit action potentials are usual.

In reinnervated muscles Weddle, Feinstein and Pattle found a decrease in the number of fibrillations occurring before the return of motor unit activity, and after the disappearance of fibrillation attempts at voluntary movement produced motor unit action potentials. This activity appears first near the point of entry of the nerve into the muscle. These potentials are at first of small amplitude but later become of greater amplitude and duration in reinnervated muscle than in normal muscle. Functional recovery is not detectable at the time that motor unit electrical activity first appears, and the time interval depends to some extent on the muscle involved. Reinnervated muscle presents small, highly polyphasic motor unit action potentials, and this type of activity is of diagnostic importance. From their data, the authors believe that neostigmine may facilitate neuromuscular transmission in the early stages of reinnervation. In the early stages of motor neuron disease the electromyographic picture resembles that produced by neostigmine in normal muscles, and similar changes are seen with progressive lesions of peripheral nerves. It is probable, therefore, that in the course of degeneration of a peripheral motor neuron there is a stage in which the myoneural junction threshold becomes decreased so that spontaneous contractions occur.

FORSTER, Philadelphia.

Psychiatry and Psychopathology

PSYCHOTHERAPY OF ALCOHOL ADDICTION IN A PRIVATE MENTAL HOSPITAL. JAMES H. WALL, Quart. J. Stud. on Alcohol **5**:547 (March) 1945.

The treatment described by Wall for addiction to alcohol is similar to that given most patients who are hospitalized for personality disorders. The patients were urged to accept as much responsibility and freedom as was possible. When a stabilizing situation in either the home or the business arose, the patient was encouraged to visit the home and resume his work. During the course of therapy, the family was given an opportunity to learn the psychologic forces involved and the methods of handling the patient.

Significant factors appeared in the study of 200 alcoholic patients. Over one-half had alcoholic relatives. Identification with them, however, seemed to be of greater importance than heredity. The men patients commonly experienced pampered, overprotected and spoiled maternal handling. The father frequently was a successful, forceful and aggressive person of whom the patient generally had a lifelong fear. Patients identified themselves with the mother, made poor sexual adjustments and acquired a feminine approach to life.

The women patients had no such familial or parental pattern but were prone to display terrific tantrums, which continued long after infancy. They commonly experienced dysmenorrhea and severe premenstrual depressions, which, no doubt, represented a resentment reaction against their femininity.

BECK, Buffalo, N. Y.

GROUP PSYCHOTHERAPY OF ALCOHOL ADDICTION. ROBERT G. HEATH, Quart. J. Stud. on Alcohol **5**:555 (March) 1945.

Although prealcoholic personalities differ basically, a few common elements are apparent. There is a desire for supremacy with self pampering, which is associated with a wish to be sheltered and to avoid responsibility. As a result

of these trends, the person finds it necessary to withdraw from society, developing what the author calls "isolationism."

A psychotherapeutic approach was adopted which was similar to that of Alcoholics Anonymous. This treatment was considered to consist of two phases: (1) establishmcnt of intellectual insight into the problem; (2) neutralization of the need for supremacy in order to remove the isolationism.

It was felt that real psychotherapeutic value was achieved by the opportunity given the alcoholic patient to expose his abnormal narcissistic personality traits. An acceptance of religion helps him combat frustration. The results of this type of treatment have been encouraging.

BECK, Buffalo, N. Y.

ALCOHOLIC HALLUCINATORY STATES. JACOB P. NORMAN, Quart. J. Stud. on Alcohol **5**:563 (March) 1945.

Norman reviewed 292 cases of so-called alcoholic hallucinosis. In approximately one third of the cases in which this diagnosis was made on admission a rediagnosis of chronic hallucinosis, schizophrenia or manic-depressive psychosis was made later. A more adequate history of the prepsychotic personality might have assisted in early diagnostic accuracy.

The case material suggested to the author that a psychosis in a young, introverted alcoholic addict often produced a schizophrenic-like reaction, with a poor prognosis. Excessive drinking by an extroverted person, on the other hand, may produce a manic-like psychosis with a favorable outlook.

Electroshock treatment appeared to have been of limited value.

BECK, Buffalo, N. Y.

ANOREXIA NERVOSA, WITH SPECIAL REGARD TO INSULIN THERAPY. D. C. WILSON, DOROTA RYMARKIEWICZOWA and W. M. WHITE, South. M. J. **39**:408 (May) 1946.

Wilson and his associates studied 10 patients with anorexia nervosa. The results with the Rorschach tests could practically be superimposed, one on the other, as the responses were practically identical. They indicated immaturity and suggested that the emotional development of these patients was checked at puberty. Deep insulin shocks were given to 5 of these patients until the habit of anorexia was broken. They gained weight, the appetite improved and they ate normally, but there was no fundamental personality change. When compared with the 5 patients in whom psychotherapy without shock was used, they seemed to be more deficient in insight at the time of discharge. This result seems to indicate that anorexia is not an incipient or mild form of schizophrenic reaction. Also, deep insulin shock may be used in cases of anorexia nervosa to check the refusal of food by the gastrointestinal system, but this must be followed by extensive psychotherapy if treatment is to be successful.

J. A. M. A.

PERSONALITY DEFECTS AND PSYCHIATRIC SYMPTOMS AFTER CEREBROSPINAL FEVER IN CHILDHOOD: MENINGOCOCCIC ENCEPHALOPATHY. M. NARASIMHA PAI, J. Ment. Sc. **92**:389 (April) 1946.

Narasimha Pai studied 29 patients with residual neuropsychiatric symptoms after an attack of cerebrospinal meningitis in early life. The majority of the patients showed personality defects. They were backward in their studies and had difficulties of adaptation at school and, later, at work. They were unstable, dependent and restricted in their interests and showed tendencies to invalidism. The patients with a family history of instability showed severe and persistent reac-

tions after recovery from the cerebrospinal meningitis. Nearly all showed tendencies to neurotic breakdown under conditions of even moderate stress. Between complete recovery and advanced dementia there may be various grades of residual disability. A group of symptoms occurs with sufficient frequency to warrant the name of meningococcic encephalopathy. This syndrome consists mainly of changes in personality, intellectual deterioration, mild but prolonged depression, headaches and a pronounced tendency to invalidism.

J. A. M. A.

Diseases of the Spinal Cord

Effect of Fatigue, Chilling and Mechanical Trauma on Resistance to Experimental Poliomyelitis. S. O. Levinson, A. Milzer and P. Lewin, Am. J. Hyg. **42**:204 (Sept.) 1945.

Levinson and his associates found that monkeys subjected to exhausting exercise or to chilling during the incubation period of experimental poliomyelitis showed a higher incidence of, and severer, paralysis than the controls. Monkeys subjected to trauma of one or more limbs during the incubation period of experimental poliomyelitis showed no correlation with the location of the paralysis, and the paralysis did not differ in severity or extent from that in the controls. The incidence and severity of paralysis was significantly greater in monkeys inoculated with the virus during the summer months.

J. A. M. A.

Poliomyelitis and Acute Gastrointestinal Upsets. W. R. Kovar, Nebraska M. J. **30**:394 (Nov.) 1945.

Kovar observed an acute clinical condition with symptoms and signs similar to those of the preparalytic stage of acute anterior poliomyelitis. The condition made its appearance during the epidemic periods of poliomyelitis in Nebraska and in the years of severe drought and economic depression. There were fever, drowsiness, headache, pain and slight rigidity of the neck, pain and some rigidity of the spine and pain in the legs. The spinal fluid was normal. The author concluded that the condition was gastrointestinal in origin and that the preparalytic symptoms of poliomyelitis were the result of deficiency in the vitamin B complex. He describes 3 typical cases and stresses that acute toxic gastrointestinal upsets are capable of producing symptoms similar to those of the preparalytic stage of poliomyelitis, due basically to deficiency in the vitamin B complex and subclinical acute beriberi. All patients with simple acute gastrointestinal conditions encountered during epidemic periods of poliomyelitis should be given large doses of the vitamin B complex. These substances are also indicated as an adjunct to treatment of all acute debilitating diseases, especially diarrheas. It is suggested that if tonsils are to be removed during the poliomyelitis season, a high intake of the vitamin B complex be insured both before and after operation. Many so-called abortive cases of poliomyelitis may be in reality an acute gastrointestinal condition characterized by symptoms of avitaminosis B. The vitamin B complex plays an important part in the etiology of poliomyelitis, and the nutritional aspect of poliomyelitis should be thoroughly investigated.

J. A. M. A.

Fibrotic Tuberculosis of the Cauda Equina. T. Alajouanine and R. Thurel, Rev. neurol. **77**:155 (May-June) 1945.

Alajouanine and Thurel state that they have been unable to find a case similar to theirs in the literature. A woman aged 50 became ill in 1940 with pain in and

hyperalgesia of the left big toe. About two years later she complained of pain in the left heel, with gradual radiation up to the buttock and the lumbar region on that side. During March 1943 she had a febrile episode with exacerbation of pain. This was followed by remission except for the persistence of pain in the left large toe. During September 1944 she again became worse. This time the pain was noted especially anteriorly in the region of the lumbar dermatomes. During December 1944 motor weakness appeared and progressed rapidly; on Jan. 26, 1945 the left lower limb was almost completely paralyzed except for some movement of the toes. The knee and ankle jerks and the plantar reflexes were not elicited on the left side; there were sensory changes on the left from the third lumbar to the fifth sacral dermatome. There were also sphincteric disturbances. Examination after injection of iodized poppyseed oil showed no block. There were 46 lymphocytes per cubic millimeter in the spinal fluid; the Pandy reaction was positive; the protein was increased, and the Wassermann reaction of the fluid was negative. A laminectomy was done on Feb. 9, 1945 at the level of the second, third and fourth lumbar vertebrae. The roots of the cauda equina on the left side were observed to be enmeshed in fibrous tissue; the roots could not be separated. Biopsy of the fibrotic tissue showed tuberculosis. Operative intervention had no effect on the course of the illness.

N. Savitsky, New York.

Schistosomiasis of the Spinal Cord. C. Gama and J. Marques de Sa, Arq. de neuro-psiquiat. **3**:334 (Dec.) 1945.

Gama and Marques de Sa report the case of a white man aged 42 who became ill with fever and a grippal syndrome, which lasted about a month. Gonococci were identified on prostatic massage. The patient was given about 600,000 units of penicillin, after which he began to complain of pain in the lumbar, pleural and abdominal regions and of formications in the lower limbs. Eight days after onset of the pains he became paraplegic, with retention of urine and feces. On admission to the hospital, he was paraplegic; the knee and ankle jerks and the abdominal, cremasteric and plantar reflexes were all absent. There was diminished sensation for pain and temperature in the lower limbs; touch and deep sensibility were spared. The Wassermann reaction of the blood was negative. There were 16 per cent eosinophils in the blood. The sedimentation time was 6 mm. in three hours. Lumbar puncture revealed partial block and xanthochromia. There were 216 cells per cubic millimeter in the spinal fluid, 95 per cent of which were lymphocytes; the total protein was 80 mg. per hundred cubic centimeters. Injection of iodized poppyseed oil showed some stoppage at the sixth thoracic and a more complete level at the twelfth thoracic dermatome. Later repetition of injection of the iodized oil showed complete block at the second lumbar segment. A laminectomy was done at the level of the first, second and third lumbar vertebrae, and an intramedullary tumor was observed. Microscopic examination showed it to be a granuloma containing eggs of Schistosoma mansoni; there were areas of necrosis in the granuloma and many eosinophils among the infiltrating cells. The patient was given antimony and roentgen therapy. Three weeks after the operation he began to move his toes, and there was some return of sphincteric control.

N. Savitsky, New York.

Cystic Hematuric Form of Poliomyelitis. F. Albert, R. J. Abuin Figueroa and M. Blanco, Semana méd. **52**:343 (Aug. 30) 1945.

Hematuria complicating poliomyelitis has been previously reported only in the preagonal stage. Albert and his collaborators observed hematuria in several

patients during the 1942 epidemic. Patients with hematuria presented also paraplegia of the legs, alone or associated with paresis of the arms. The consequent atrophy of the legs was severe. The patients did not have dysuria or renal or gastrointestinal disorders. The course of the neuromuscular lesions was not influenced by the hematuria. The general condition of patients in the course of the hematuric phase was good. Hematuria as a complication of poliomyelitis occurred within the first month of the disease. The urine was normal except for the presence of blood. Some cases of hematuria were complicated by urinary retention. Catheterization in these cases was not followed by hematuria. The blood pressure was normal. In some cases hematuria reappeared after several days of normal urinary secretion. The prognosis is benign, as hematuria, both primary and recurrent, disappears spontaneously and without treatment. The authors believe that this form of hematuria depends on a selective localization of the poliomyelitis virus in nerve tissues which elicit a transient neurogenic reaction of the bladder, with consequent hematuria.

J. A. M. A.

Treatment, Neurosurgery

USE OF PENICILLIN IN THE TREATMENT OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM, J. LAMAR CALLAWAY, RAY O. NOOJIN, ARTHUR H. FLOWER, BEATRICE H. KUHN and KATHLEEN A. RILEY, Am. J. Syph., Gonor. & Ven. Dis. **30**:110, 1946.

Data are presented on 100 unselected patients who had active neurosyphilis and were treated with penicillin. The patients had a positive Wassermann reaction of the spinal fluid, an increase in cells in the spinal fluid and/or an increase in the total proteins of the spinal fluid, together with clinical symptoms and signs. The series includes both white and Negro, private and ward, patients. Eighty-five patients were male; 15 were female. Eighty-two were white, and 18 were Negro. Seventy-eight of the patients were between the ages of 20 and 49 years.

All patients, regardless of the type of neurosyphilis, were treated experimentally with a total dose of 4,000,000 Oxford units of penicillin introduced intramuscularly in isotonic solution of sodium chloride over a ten day period. Sixty per cent of the patients showed clinical improvement associated with definite improvement in the spinal fluid findings; 31 per cent, clinical improvement alone; 4 per cent, improvement in the spinal fluid findings unassociated with clinical change, and 5 per cent, decided clinical deterioration with no improvement or progression in their spinal fluid findings. After treatment, 8 per cent of the total had negative Wassermann reactions of the spinal fluid.

The patients with no previous therapy apparently responded best to penicillin, while those with previous adequate chemotherapy showed the poorest response. Previous fever therapy given more than six months before penicillin therapy exerted no effect on the response to penicillin.

Febrile Herxheimer reactions were frequent, but there were no reactions necessitating the termination of therapy. Extreme care should be taken with patients who have concomitant cardiovascular syphilis, in order to prevent serious Herxheimer reactions.

Although no definite conclusions can be established, a favorable therapeutic trend is indicated.

"To paraphrase Stokes and his co-workers, we feel that the results with penicillin therapy will for the moment, in the limited period of observation, bear comparison with those of fever therapy. It has, in our experience, produced transformations, symptomatically and serologically, without serious reactions or serious

inconvenience to the patient. Its effect has been equal to or superior to those obtained by longer, more expensive, more reactive fever therapy, arsenotherapy or treatment with heavy metals. Combinations of fever with penicillin in varying schemes of treatment may prove more valuable than either alone."

GUTTMAN, Philadelphia.

AN ANALYSIS OF COMPLICATIONS ENCOUNTERED DURING THERAPEUTIC MALARIA. HILTON S. READ, LAWRENCE I. KAPLAN, FREDERIC T. BECKER and MARK F. BOYD, Ann. Int. Med. **24**:444 (March) 1946.

The authors report observations on 300 patients who were subjected to malaria for the treatment of neurosyphilis. Seventy-five per cent of the patients had asymptomatic neurosyphilis and were in excellent physical condition. Although racial immunity, previous attacks of natural malaria and the recent return of some patients from hyperendemic areas necessitated a number of reinoculations with heterologous malarial strains, 211 patients finally completed therapy with Plasmodium vivax and 89 with Plasmodium malariae.

The usual clinical features of malaria, namely, anemia, lowered blood pressure, herpes simplex, gastrointestinal distress, muscular pain, cough and loss of weight, are not considered in detail because of their relative benignity and their constancy of appearance during active febrile disease.

Jaundice, edema, mild renal damage and neural syndromes are relatively common features of untreated malarial infection. Though they presented clinical problems during active therapy, none was followed by permanent sequelae.

Hepatitis with jaundice can at times be adequately controlled by intravenous injection of fluids and a diet high in carbohydrate and protein without necessitating the interruption of malaria; but in most cases such interruption is indicated, at least temporarily. With active treatment, no case of jaundice persisted more than fifteen days. Excessive corpuscular hemolysis in the absence of impaired hepatic function accounted for almost 50 per cent of the cases in which icterus developed. The accidental transmission of a hepatotoxic agent with the inoculation of plasmodia into the blood, observed in 2 instances in this series, may play an important role in the "malarial" hepatitis observed during the therapy of neurosyphilis. Recent studies of homologous serum jaundice as differentiated from catarrhal jaundice (infectious hepatitis) may clarify this observation in the future. The occurrence of the complication, however, in mosquito-inoculated patients attests, at least in some instances, to a more specific toxic effect of malaria on the liver. Predisposing hepatic damage by prolonged arsenical therapy or rare syphilitic involvement of this organ cannot readily be evaluated. The constantly positive results in cephalin flocculation tests in cases of malaria adds to the growing impression that this reaction is nonspecific.

Although the causes of edema during active malaria may be multiple, hypoalbuminemia is probably the precipitating factor in most cases. Three cases of edema, with no adequate clinical or laboratory etiologic explanation, are reported. The duration of edema did not exceed thirty days, and in most instances proper diet proved to be adequate therapy.

Episodes of albuminuria and hematuria during repeated malarial attacks may play a role in the production of chronic recurrent focal nephritis. Abnormal urinary findings improved spontaneously during malarial activity in almost 25 per cent of the cases in which they appeared and did not last longer than thirty-one days in any case once antimalarial therapy was instituted. Malaria is to be considered an etiologic factor in acute nephritis, 4 cases of which were observed in this series.

The neurologic and psychiatric manifestations of malaria due to P. vivax and P. malariae are relatively benign and readily amenable to antimalarial therapy. Two mental complications, one an agitated psychosis and the other an acute hallucinatory syndrome, may have been related to the administration of quinacrine (atabrine).

An unusual form of severe respiratory distress with cyanosis was observed in 2 instances. It was also found that bronchial asthma is greatly aggravated during malarial paroxysms. The authors describe unusual cases of purpura, herpes zoster ophthalmicus, urticaria, hyperlipemia, spontaneous splenic rupture and hypocalcemic tetany complicating malarial infection. Fatalities, the only 2 in this series of 300 malaria-treated patients, occurred in the last 2 cases.

Although it is recognized that the course of repeated paroxysms in therapeutic malaria differs from that of natural malaria interrupted early in its cycle by antimalarial agents, the use of malaria therapy presents an opportunity for the clinical study of the diverse manifestations of a disease which, because of extensive military operations in hyperendemic areas, may occupy the national health stage for many years.

GUTTMAN, Philadelphia.

THROMBOSIS OF A CAVERNOUS SINUS TREATED WITH PENICILLIN AND HEPARIN. ROBERT HENNER and EARLE G. RIDALL, Arch. Otolaryng. **41**:295 (April) 1945.

Henner and Ridall report the case of a young man who was brought into the hospital with herpes of the lips and nose, cellulitis of the nose and a mild acute infection of the upper respiratory tract. The infection spread rapidly, and on the second day of hospitalization a blood culture yielded a growth of Staphylococcus aureus. Thrombosis of the cavernous sinus developed, and by the third day the patient was stuporous. Treatment with sulfadiazine from the time of admission seemed to be ineffective. Penicillin therapy was instituted, with intravenous injection of heparin at intervals. By the fifth day improvement was noted. A blood culture on the seventh day of hospitalization yielded no growth of organisms. Motion of the right eyeball began to return, and by the twelfth day external ocular movements were normal. Penicillin therapy was discontinued on the seventeenth day, and by the forty-second day the patient was completely cured. The use of heparin seemed to enhance the availability of penicillin by increasing the coagulation time of the blood. The response to penicillin of this infection with Staph. aureus suggests the possibility of producing more cures in cases of other infections caused by sulfonamide-resistant organisms.

RYAN, Philadelphia.

APICAL PETROSITIS: MEDICAL AND SURGICAL MANAGEMENT IN CASES WITH AND WITHOUT COMPLICATING MENINGITIS. WILLIAM C. THORNELL and HENRY L. WILLIAMS, Arch. Otolaryng. **43**:393 (April) 1946.

Though they well recognize that each case must be approached as an individual problem, Thornell and Williams outline the medical and surgical management of cases of petrositis with or without complicating meningitis. Before operation on the petrous pyramid, the complicating meningitis should be well controlled and the patient in the best possible physical condition. The use of sulfadiazine in conjunction with penicillin is strongly advocated. Care should be exercised to maintain an adequate intake and output of fluids in the use of such large doses of sulfadiazine. Adequate alkalization must also be considered to prevent renal complications. Intrathecal administration of penicillin in cases of meningitis is a valuable adjunct to other means of administration.

Reliance on chemotherapy alone is dangerous. Because of the frequency of intracranial extension from apicitis, adequate drainage must be established when symptoms of involvement of the petrous pyramid develop in the presence of an

apparently adequately draining ear. Drainage of the suppurative foci in the petrous pyramid should be accomplished in two stages. The perilabyrinthine region should be first explored; then, if necessary, a complete apicectomy may be done, preferably by the Ramadier-Lempert technic.

RYAN, Philadelphia.

MIGRAINE: ITS TREATMENT WITH PROSTIGMINE BROMIDE. I. J. PATTON, Canad. M. A. J. **54**:588 (June) 1946.

Patton used neostigmine bromide in the treatment of 6 patients with histories of migraine of from eight to twenty-five years' duration. Two patients reported moderate improvement; 3, great improvement, and 1 declared it was "a miracle." One 15 mg. tablet of neostigmine bromide is dissolved in 1 ounce (30 cc.) of distilled water. The patient is instructed to take the drug three times daily, beginning with 1 drop and increasing each dose by 1 drop until she is taking 10 drops three times a day. After continuing on this dosage for one week, the patient drops to a maintenance dose of 10 drops twice weekly, and if signs of impending headache are noticed she takes an additional 15 to 20 drops.

J. A. M. A.

USE OF NEOSTIGMINE (PROSTIGMINE) IN SUBACUTE POLIOMYELITIS. C. J. FRANKEL and R. V. FUNSTEN, South. M. J. **39**:482 (June) 1946.

Frankel and Funsten report on 58 patients with subacute poliomyelitis between the ages of 6 months and 42 years. All the patients showed variable amounts of muscular spasm; 8 presented pronounced incoordination and 4 moderate incoordination. Eight patients had contractures or conditions in which joints could not be moved without undue force or pain. Oral administration of neostigmine bromide was disappointing and was discontinued. Neostigmine methylsulfate, given subcutaneously in doses of 1.5 to 2 mg. for adults and 0.5 to 1 mg. for children, proved effective. Forty-six patients (80 per cent) showed improvement to normal ranges of passive motion in from three to eighteen weeks of treatment. Seventeen patients (30 per cent) showed dramatic improvement in from one to four days. Twelve patients (20 per cent) showed little or no improvement. Twenty-three patients showed good results only after treatment was interrupted for from five to seven days and then repeated. All patients with muscular incoordination showed definite improvement. None of the patients had permanent contractures. The patients became ambulatory more rapidly, and the period of hospitalization could be cut down. The return of active muscular power did not seem to be influenced by the drug. Treatment with this drug can be, and probably should be, combined with modified hot pack therapy.

J. A. M. A.

SURGICAL TREATMENT OF VASCULAR ANOMALIES OF THE PREMOTOR AREA PRODUCING EPILEPSY. F. L. REICHERT, Surgery **19**:703 (May) 1946.

Fifteen patients were treated for epileptic seizures due to vascular anomalies in the premotor region. The follow-up period was at least five years. The treatment consisted in coagulation of the vascular lesions, and the results indicate that the procedure was feasible and satisfactory. Nine of the 15 patients had premotor signs. Six patients, besides having the cortical vascular anomalies, had one or more dural angiomas. Four patients had cortical angiomas or hemangiomas. Three were proved to have callosal angiomas by ventricular needle puncture. In these 3 cases of callosal angiomas the ventriculograms showed a new sign of separation of the bodies of the ventricles. Coagulation of the abnormal vessels frequently produced a transient hemiplegia until normal collateral vascular channels developed. Subtemporal decompression made a smoother convalescence if employed when there

was disturbance of cortical circulation resulting from coagulation. Intravenous injection of hypertonic solutions aided in overcoming the cerebral edema that followed the disturbance of circulation incident to the operative coagulation. Two of the 15 patients had only temporary relief from seizures; 7 had milder and less frequent attacks, and 6 had no seizures after operation.

J. A. M. A.

CARE OF THE PARAPLEGIC'S URINARY TRACT. M. H. NOURSE and H. C. BUMPUS, U. S. Nav. M. Bull. **46**:1053 (July) 1946.

Consequent to trauma to the spinal cord, after a few months, the bladder wall thickens, there is a tendency toward spasticity of the musculature, and the mucosa shows increased trabeculation. Inadvertently, the bladder becomes overdistended, injuring the tone of the muscle, subjecting the bladder to trauma from overdistention in general surgical procedures and invariably leading to febrile reactions when catheterization at regular intervals is resorted to. The authors apply the same criticism to tidal drainage. In cases of battle casualties, in which various methods of transportation must be considered, a suprapubic drain is the only insurance against obstruction and infection. Much, however, favors the use of urethral drainage in civilian medicine or paraplegic centers, where adequate observation and nursing care are available.

The automatic bladder of infancy or injury to the cord is controlled via a reflex arc in the conus medullaris in the region of the twelfth thoracic and the first lumbar segment. Voluntary control of the bladder in adult life is the result of development of a pathway for the passage of inhibitory impulses from higher centers. Trauma to this pathway results after a few months in the development of an automatic bladder. There is a rough correlation between the height of injury in the cord and the resulting bladder function established. A more or less efficient automatic bladder may be expected from a high lesion in the cord, and in the case of a casualty in the lower lumbar region of the spine ultimate voluntary control is possible.

In the spastic bladder, the ability of the detrusor muscles to overcome the obstruction of spastic sphincters governs the satisfactory emptying of the bladder. Transurethral resection for the removal of this obstruction enables certain of both the automatic and the voluntary types of function.

Automatically functioning bladders were present in 37 of the 87 cases of paraplegic casualties among sailors and Marines in the authors' series. In 16 of these cases transurethral resection was necessary for efficient action. In the other 21 cases a minimal residuum of urine of not more than 2 ounces (59 cc.) may be present most of the time. Resection of the tissue of the neck of the bladder is reserved for cases in which the patient is unable to expel any urine or in which many ounces of residual urine remain. Streptomycin has been valuable in the control of infection with residual urine.

Voluntary control or initiation of micturition in cases of complete severance of the cord above the conus has not been observed, nor have the authors seen cases of conditioned reflexes in which the patient strokes his thighs and the bladder empties. By proper modeling of the muscles of the bladder neck through transurethral resection (29 cases), voluntary function was obtained with injuries below the conus.

Healing following resection is slow in cases of paraplegia, and late bleeding is often a complication.

Another complication in the care of the paraplegic patient is hypercalcinuria. Routine roentgenographic and cystoscopic examinations are necessary for discovery of stones because of the insensitivity of the urinary tract. An elevation of temperature is usually the first sign of calculus obstructing the tract. With preventive measures, which include large fluid intake, frequent change in position of the patient and acidification of the urine by means of mandelic acid, calculi in the upper part of the tract have been observed in only 14 of the 87 cases.

BERRY, Philadelphia.

POSTERIOR COMMISSURAL MYELOTOMY FOR TABETIC GASTRIC CRISES. J. CHRISTOPHE and J. GUILLAUME, Rev. neurol. **77**:78 (March-April) 1945.

Christophe and Guillaume treated a man aged 50 who had had gastric crises every year for fifteen years. The pupils showed mild mydriasis, with no reaction to light or in accommodation. The ankle jerk was absent. There was mild ataxia in the lower limbs. Prior to the operation he had had a severe crisis of about seven weeks' duration. The Wassermann reactions of the blood and the spinal fluid were negative. On June 28, 1944, a laminectomy was done at the level of the first to the fourth dorsal segments, inclusive. An incision was made into the cord strictly in the midline after separation of Goll's columns. The entire thickness of the cord was incised. The pain disappeared immediately after the operation. The patient had to be catheterized for a few days. For a short time he noted numbness of the feet. There was mild diminution of sensation for pain and temperature from the fifth to the seventh dorsal segment, inclusive; these sensory changes disappeared in a month. On Feb. 1, 1945, the authors stated that the "patient recently reported that the pain had not recurred." There were no new neurologic findings.

N. SAVITSKY, New York.

MENTAL CHANGES ACCOMPANYING ABORTIVE HYPERTHYROIDISM: TREATMENT WITH SHOCK. FLAVIA DE SOUZA, Arch. brasil. de med. **35**:199 (July-Aug.) 1945.

De Souza reports 2 cases in which mental symptoms accompanying hyperthyroidism cleared up after shock therapy. The first patient, a girl aged 16, presented evidence of hyperthyroidism, extreme emotional lability, ranging from exultation to depression, hypomanic behavior, insomnia, anorexia and bizarre mental content. Eight metrazol treatments were given, after which the mental symptoms cleared up. Treatment for her thyroid disturbance was continued after the mental symptoms disappeared. The second patient, a white woman aged 40, in addition to hyperthyroidism, presented the clinical picture of a depression, with suicidal ideas, indecisiveness, loss of interest, inability to work and feelings of mental insufficiency. She had been incapacitated for eight months because of the mental symptoms. Six metrazol treatments were given, and the mental symptoms cleared up. The author concludes that hyperthyroidism is not a contraindication to shock therapy provided there is no serious impairment of the circulatory apparatus. He adds that treatment for the hyperthyroidism should be continued after the shock therapy.

N. SAVITSKY, New York.

ACCIDENTS AND COMPLICATIONS OF CONVULSIVE THERAPY. E. ARRUDA, Arq. brasil. de neurol. e psiquiat. **25**:33 (Jan.-March) 1946.

Arruda refers to his own experiences but gives no statistics. He states that temporomandibular luxation is the most common complication of convulsive therapy and that it is due to very wide opening of the mouth. Luxation of the shoulder is due to sudden abduction and elevation of the arms. In 1 case in his series there was fracture of the lower jaw. There were no vertebral fractures. The author mentions cases of cardiovascular collapse which came on fifteen to twenty minutes after induction of the shock, with weakness, cold extremities, pallor and chills. He cites an unpublished case of a colleague in which a spinal hemorrhage developed after convulsive therapy. He reports a case of gangrene in the region of the antecubital fossa resulting from infiltration of metrazol into the tissues. In 1 case a burn occurred at the site of application of electrodes. Hyperthyroidism became

evident in 1 case after convulsive therapy (probably metrazol). He comments on the probability that terror or fear of injection may have precipitated the hyperthyroidism. The appearance of amyotrophic lateral sclerosis in a woman aged 40 after shock therapy is considered as having been due to the shock. Two cases of pulmonary tuberculosis are cited in which the disease became active after treatment. The author points out the value of roentgenographic examination of the chest before treatment. He does not approve of the use of curare, for it increases the risk and does not entirely prevent fractures. He describes a method of preventing dislocation of the jaw by placing one assistant at the patient's head with the palm of one hand against the chin, exerting pressure during the seizure, while the other hand keeps the gag from being pushed out by the tongue. He does not believe that a pillow placed beneath the patient prevents fracture of the vertebrae. In 1 case muscular twitching, which persisted for a few hours after a metrazol convulsion, cleared up with 2 cc. of "somnifene" (diethyl-diallyl barbiturate of diethylamine) administered intravenously.

N. SAVITSKY, New York.

TUBERCULOMA OF THE BRAIN: SURGICAL EXCISION. TOLOSA, TENUTO and DA SILVA JR., Arq. de neuro-psiquiat. **4**:28 (March) 1946.

A single laborer aged 21 gave a history of jacksonian attacks on the left side and headaches of a few months' duration. Examination showed bilateral papilledema and weakness of the left side of the face. Lumbar puncture revealed an initial pressure of 40 mm.; the total protein was 40 mg. per hundred cubic centimeters. Ventriculographic examination revealed a tumor in the right frontoparietal region. At operation, performed on Oct. 20, 1944, three small tumors, the size of olives, were removed. Histologic examination revealed them to be tuberculoma. After the operation there were some accentuation of the facial weakness and dysstereognosis on the left side. On the sixth postoperative day the temperature rose. There was roentgenographic evidence of pulmonary tuberculosis. The patient died of pulmonary tuberculosis in June 1945. There was no recurrence of the cerebral lesions. Roentgenograms of the lungs were not obtained before operation. The authors note that tuberculomas can be operated on, like other tumors of the brain, if the general condition does not contraindicate such intervention.

N. SAVITSKY, New York.

PENICILLIN TREATMENT OF SIX PATIENTS WITH NEUROSYPHILIS WHO HAD HAD MALARIAL THERAPY. P. W. LONGO, M. ROBORTELLA and J. B. DOS REIS, Arq. de neuro-psiquiat. **4**:47 (March) 1946.

The authors report their experience with penicillin in treatment of 3 patients with dementia paralytica, 2 patients with the tabetic form of dementia paralytica and 1 patient with neurosyphilis with convulsions. The minimum duration of the illness was one year; 1 patient had been ill five years and another ten years. Intrathecal injections were given every forty-eight hours, and 20,000 to 25,000 units of penicillin was administered intramuscularly every three hours. One patient received only intramuscular injections, with good results. In 2 patients the meningeal reaction was so severe that intrathecal injections had to be abandoned. Two patients had transitory confusion. One patient had severe convulsions during treatment, but convulsions were present before therapy was begun. Two patients exhibited notable improvement in behavior after treatment. One patient showed less irritability. For 3 other patients the results were inconclusive. In 1 case the total protein became diminished during treatment and precipitation in the first part

of the colloidal gold test became less pronounced, though the Wassermann reaction continued to be positive. Cellular responses to intrathecal injection of penicillin were noted in 2 patients.

N. Savitsky, New York.

Penicillin Therapy of Syphilitic Atrophy of the Optic Nerve. P. W. Longo and J. M. Taques Bittencourt, Arq. de neuro-psiquiat. **4**:55 (March) 1946.

The patient, a man, began to find it difficult to distinguish colors in August 1944. In January 1945 he noted a definite decrease in visual acuity and in May could not recognize people at 3 meters. In August he had difficulty in reading. Examination on August 16 showed that the pupils were equal and regular and reacted in accommodation but not to light. There were primary atrophy of the optic nerves, diminished vision and ability to count fingers at 4 meters. The fields showed definite concentric contraction. The knee and ankle jerks were not elicited. The spinal fluid was clear, with 48 cells per cubic millimeter, of which 10 per cent were monocytes and 90 per cent lymphocytes. The Wassermann reaction of the spinal fluid was positive. Treatment was begun on August 17 and was continued for eleven days. The total dose was 2,500,000 Oxford units of penicillin; 20,000 units was given every hour intramuscularly. During the first two days 20,000 units was given intrathecally every day. From the third to the ninth day the dose was increased about 10,000 units per day. Lumbar puncture was done daily during treatment. There was no increase in pressure; the total protein and the cell count were slightly increased, especially the monocytes. Thirty days after treatment the total protein was decreased and the Pandy and Wassermann tests were less positive. Visual acuity improved from 0.1 to 0.15. The visual fields became definitely wider. The achromatopsia persisted.

N. Savitsky, New York.

Intrathecal Penicillin Therapy: Immediate and Late Reactions. J. M. Taques Bittencourt, J. A. Caetano da Silva Jor and H. M. Canelas, Arq. de neuro-psiquiat. **4**:68 (March) 1946.

The authors report complications of intrathecal injection of penicillin in 17 cases of syphilis, 11 cases of dementia paralytica, 2 cases of tabes, 2 cases of syphilitic optic neuritis, 1 case of syphilitic myeloradiculitis and 1 case of syphilitic osteitis. The penicillin was given suboccipitally in 14 cases and by the lumbar route in 3 cases. It was given daily in all cases, beginning with 20,000 units and increasing by 10,000 units per day up to a dose of 100,000 units in each injection. The total dose administered intrathecally varied from 250,000 to 700,000 units. Each patient had eight to eleven injections. The immediate reactions were as follows: (1) sensations of heat, and more rarely of cold, in the parietotemporofrontal region in all cases in which the injections were given suboccipitally; (2) fleeting headache, usually frontal, in all such cases, and (3) vomiting and nausea in 35 per cent of the total series of cases. The usual late reactions were: (1) lumbar radicular pain, lasting a few hours after the injections, in all cases in which the lumbar route was used; (2) frontal headaches, lasting more than four hours, in 30 per cent of all the cases, and (3) an increase in temperature to 38 C. (100.4 F.) for a few hours after injections in 12 per cent of the cases. Rare late reactions were: (1) diffuse perspiration, changes in pulse, visual disturbances, torpidity and even loss of consciousness, in 3 cases; (2) fine tremors, especially in the upper limbs, lasting about an hour, in 2 cases; (3) delirium with visual hallucinations and motor agita-

tion, in 1 case, and (4) a cauda equina syndrome with perianal anesthesia and sphincteric disturbances, lasting over a month, in 1 case. The worst reactions were noted with doses of more than 50,000 units. No relation was observed between the reactions and the duration of the penicillin therapy. The authors believe that impurities in the penicillin preparation were a factor in some of the reactions.

N. SAVITSKY, New York.

SURGICAL TREATMENT OF PAIN OF THE TRIGEMINAL NERVE: RETROGASSERIAN NEUROTOMY BY TEMPORAL INTRADURAL ROUTE. J. RIBE PORTUGAL, Hospital, Rio de Janeiro **29**:501 (April) 1946.

Ribe Portugal divides surgical operations on the trigeminal nerve into four groups: (1) on the peripheral branches, (2) on the gasserian ganglion, (3) on the dorsal roots and (4) on the cerebral trunk. He describes an incision giving access to the trigeminal nerve at the pons Varolii. He explains his technic for sectioning the trigeminal nerve by the temporal intradural route, that is, by opening the dura, elevating the temporal lobe and opening Meckel's cavity or sectioning the tentorium. He prefers opening Meckel's cavity because the tentorium supports the cerebrum. Both operative procedures are easy, avoiding trauma of the gasserian ganglion and not provoking bleeding. He presents 20 illustrative case histories from among the 118 cases in which he sectioned the trigeminal root by the temporal and subtentorial approach.

J. A. M. A.

EFFECT OF SYMPATHECTOMY ON PHANTOM PAINS AFTER AMPUTATION OF LIMBS. A. ELLONEN, Acta chir. Scandinav. **93**:131, 1946.

Ellonen reports 28 cases of phantom limb pain in persons who had an extremity removed. Phantom limb pain followed amputation of the femur in 10 cases, amputation of the leg in 14 cases, amputation of the foot in 2 cases and amputation of the arm in 2 cases. Sympathectomy or blocking of the sympathetic nerves was performed in 15 of these cases. Spinal anesthesia was administered in the remaining 13 cases. In 5 cases of permanent phantom limb pain ("absolute cases") complete disappearance of pain resulted from lumbar sympathectomy, and in an additional case, from cervical sympathectomy. In 1 case lumbar ganglionectomy, blocking of the sympathetic nerve and resection of the sciatic nerve proved ineffective, while disappearance of pain resulted from repeated spinal anesthesia. In 6 cases definite recovery from temporary phantom limb pain ("relative cases") resulted from blocking the sympathetic nerve. Blocking was obtained with 30 cc. of a 1 per cent solution of procaine hydrochloride. Spinal anesthesia was administered in 12 cases and proved ineffective in all.

J. A. M. A.

SURGICAL TREATMENT OF SCLERODERMA. M. HÄMÄLÄINEN and B. SÖDERLUND, Acta chir. Scandinav. **93**:201, 1946.

Hämäläinen and Söderlund report 4 cases of scleroderma in which sympathectomy was carried out at the district hospital of Kuopio, Finland. The patients were a man aged 28, 2 women aged 38 and a girl aged 12 years. The follow-up time in these cases was one and one-half years. The results have so far been satisfactory. It is concluded that scleroderma should not be considered an incurable disease and that surgical treatment is warranted. Disturbances of calcium metabolism were not present in these cases. Sympathectomy is to be preferred to parathyroidectomy, which is associated with greater risk.

J. A. M. A.

Muscular System

PRIMARY MYOPATHY CHARACTERIZED BY "MICROPYGIA" IN THE FIRST GENERATION AND SCAPULOHUMERAL DYSTROPHY IN SECOND ONE OF CONSANGUINEOUS PARENTS. S. MATUS, South African M. J. **20**:170 (April 13) 1946.

Matus reports the occurrence of familial primary myopathy in a man aged 46 and in his 2 sons, aged 5 and 6 years respectively. The 2 children presented a muscular atrophy of the pure scapulohumeral type. The supraspinous and infraspinous fossae were nearly devoid of any muscle, and the spine of the scapula was forming a visible ridge under the skin. The deltoid and the pectoral muscles were involved. The manifest atrophy of the serratus contributed to the "winged scapulas" and gave to the children a peculiar attitude, conspicuous by the "dropped shoulders" and the protruding abdomen. A scoliotic spine completed the clinical picture. The father of the 2 boys presented an unusually small buttock with pronounced atrophy of the gluteal muscles, for which the term "micropygia" was coined by the author. The smallness of the buttock was accentuated by the adiposity above (pseudohypertrophy of the upper part of the gluteal muscles). The collateral history of the man revealed that his cousin, the daughter of the middle-aged brother of his father, had the same "micropygia." The familial origin of this muscular dystrophy was further evidenced by the fact that his wife is his cousin, the daughter of the youngest brother of his father, while he is the son of the oldest brother.

J. A. M. A.

MYOTONIA CONGENITA (THOMSEN'S DISEASE): THERAPEUTIC CONSIDERATIONS. P. PUPO, J. G. MEIRA and J. NASSER, Arq. de neuro-psiquiat. **4**:1 (March) 1946.

The authors report studies on a Brazilian aged 21 of Italian descent, with no family history of nervous or mental disease. The diagnosis of myotonia congenita was definite, the illness having been present since the seventh or eighth year of life. There was no involvement of the cardiac or the ocular muscles. Electrical reactions and the electromyographic and ergographic findings were typical of the disease. On two occasions, thirty days apart, twenty minutes after the intramuscular injection of 1 cc. of solution of epinephrine hydrochloride myotonic reactions almost disappeared for about twenty-five minutes. Intramuscular injections of suspension of epinephrine in oil had no effect. Intravenous injections of 0.25 mg. of atropine sulfate in 10 cc. of 25 per cent dextrose had no effect on the myotonia. The oral administration of ergotamine tartrate for six days had no effect. One gram of quinine sulfate by mouth began to have an effect on the myotonia in twenty-five minutes. The myotonia disappeared completely in forty to forty-five minutes. Myotonia was absent for an average of ten hours in eight such experiments. The effects of quinine were demonstrated by moving pictures and electromyographic and ergographic studies.

N. SAVITSKY, New York.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Kenneth J. Tillotson, M.D., *Presiding*

Regular Meeting, April 18, 1946

Comparison of Epileptic Patients with Normal Electroencephalograms with Those with Abnormal Electroencephalograms. DR. JOHN A. ABBOTT.

This study is based on a group of 193 persons attending the clinic for adult epileptic patients at the Massachusetts General Hospital. As criteria for inclusion in this group, the clinical diagnosis of epilepsy was unequivocal and the electroencephalogram was taken in accordance with a well standardized procedure. Of these 193 patients, 40, or 21 per cent, had normal electroencephalograms; 20, or 10 per cent, borderline patterns, and 133, or 69 per cent, abnormal patterns.

Comparison of patients having normal electroencephalographic patterns with those having abnormal patterns revealed the following differences:

1. In general, the age of onset of chronic epilepsy was higher among patients of the first group, with normal electroencephalographic patterns, than among those of the second group, with abnormal patterns.

2. The incidence of patients having grand mal without any other type of seizures was strikingly higher in the first group than in the second group.

3. In general, seizures were less frequent among patients of the first group than among patients of the second group, with a high incidence of patients in the first group who had only one or two seizures a year.

4. Analysis of medication at the time of the last visit showed that for all kinds of anticonvulsant drugs the dose was slightly, but consistently, smaller for patients of the first group than for patients of the second group. Furthermore, at the time of the last visit, 7, or 18 per cent, of the first group had discontinued all such medication without recurrence of seizures, whereas only 2 or 3 per cent of the second group could discontinue medication.

5. Five, or 13 per cent, of the patients in the first group reported that all, or all but one, seizure occurred in sleep, whereas this was true for only 2 or 3 per cent of the patients in the second group.

6. With respect to a history of seizures in infancy or childhood, there was only a slight difference in favor of the first group, with 10 per cent of the first group and about 16 per cent of the second group showing such seizures.

7. With respect to established post-traumatic or other encephalopathy, there was, again, only a small difference in favor of the first group, with 30 per cent of the first group and about 35 per cent of the second group showing established encephalopathy other than cerebral dysrhythmia.

8. Eighteen per cent of the first group and about 26 per cent of the second group gave a positive family history for epilepsy.

9. With respect to scholastic and occupational histories, there was a considerable difference between the two groups. Of the first group only 10 per cent, whereas of the second group about 29 per cent, had experienced serious scholastic or occupational difficulties.

DISCUSSION

DR. STANLEY COBB: This is an interesting and valuable paper. All who manage epileptic patients are asked: What does it mean when a person with known epilepsy has a normal electroencephalogram? That is, the record is normal when made between attacks, but it should be emphasized that the pattern would have been abnormal during an attack.

Dr. Abbott has shown that the patients with abnormal electroencephalograms are likely to have an earlier onset of the disease, more and severer seizures and convulsions rather than petit mal attacks, and that they need more medicine to keep them free from seizures. Is there any chance that the patients having had more medicine might have made the electroencephalograms more abnormal?

In summarizing, Dr. Abbott remarked that a history of fits in infancy was rare with a normal electroencephalogram. The association was less common, but I do not think that it was rare. There is perhaps a lesson to be drawn from the slide showing that patients with abnormal tracings needed more medicine. Is one to conclude that medication can be stopped when the electroencephalogram becomes normal? That is a hard thing to decide.

DR. WILLIAM G. LENNOX: I endorse Dr. Cobb's statement that this is a worth while piece of work. Many clinicians expect every patient who has seizures to have abnormal brain waves. Perhaps the electroencephalogram was oversold at first.

I wish to commend Dr. Abbott for keeping the work within practical limits. Several years ago Dr. and Mrs. Gibbs and I listed comparable data for 1,000 patients, data which we have yet to tabulate. Dr. Abbott has presented various factors which have to do with records which are normal or abnormal. One might try to break down these factors a bit.

First, I raise the question of what constitutes an abnormal record. Dr. Abbott, probably wisely, did not try to define the normal. Recently I have been nonplused by the number of epileptic persons with normal records. Dr. and Mrs. Gibbs and I found that 16 per cent of epileptic patients examined at the Boston City Hospital had normal records. For the last 500 patients I examined at my private laboratory this proportion was 25 per cent. Perhaps private patients are better endowed with respect to their brain waves, have had less cerebral damage or have had epilepsy a shorter time, or perhaps our conception of what is normal has become more liberal.

Another factor is age. Is it age per se, or the fact that older patients have less frequent seizures? It is known that the older person, whether ill or normal, has more stabilized brain waves than the younger one. Perhaps an epileptic patient has more normal brain waves as he gets older whether he is treated or not. It is known that seizures become more infrequent as a person grows older; perhaps brain waves become more normal. We have evidence on the influence of seizures in records made on identical twins, only 1 of whom has epilepsy; that one twin has more abnormal brain waves than the nonepileptic co-twin. There is difficulty in drawing conclusions based on tabulation of the total number of seizures. Patients with petit mal have so many seizures that any average figures are distorted.

Dr. Abbott did not classify his results with respect to the degree of abnormality and the various types of electroencephalographic records. That, perhaps, would be interesting. The degree of abnormality is important with respect to the severity of the epilepsy. There, again, is a difficulty, in that patients with petit mal have a much higher incidence of abnormality in the electroencephalogram than patients with other types of seizures. That is partly because overventilation usually brings out the alternate spike and wave pattern in patients subject to petit mal.

I wonder whether Dr. Abbott would sum up the data from his last chart by saying that an epileptic patient with normal brain waves has a relatively good prognosis.

DR. ROBERT S. SCHWAB: I congratulate Dr. Abbott on his turning an unfavorable aspect of the situation into an advantage. When my colleagues and I found that 15 to 20 per cent of electroencephalograms in cases of proved epilepsy were normal, it was embarrassing to explain this to the clinician. It was not mentioned at meetings unless necessary; one was somewhat ashamed not to have the results of the examination 100 per cent in agreement with the clinical findings, like the Wassermann test for syphilis or the roentgenographic examination of the chest for tuberculosis. So many laboratories have arrived at approximately the same percentage that we have accepted it as correct.

The clinician can be informed that the patient with a normal electroencephalogram is better off than the patient with an abnormal record. He may still have epilepsy, but he has a better chance to get along; and, as Dr. Abbott has shown, he has a better chance of discontinuing medication and remaining free of seizures. Perhaps, therefore, this disadvantage of having a laboratory test that was only 80 per cent in agreement with the clinical evidence can be turned to a distinct help to the patient.

The fact that a normal electroencephalogram indicates fewer seizures, and those mainly at night, better response to anticonvulsant drugs and, finally, ability to secure employment and hold jobs is a definite prognostic advantage to any patient.

DR. MILTON GREENBLATT: I was interested in Dr. Abbott's report. I wonder whether the patients were classified according to possible factors precipitating the seizures. Some patients have convulsions in the hypoglycemic state; some, after overindulgence in alcohol, some, after a period of insomnia, fatigue, exertion or emotional upset. Would an analysis on the basis of these factors have revealed any difference in the incidence of electroencephalographic abnormality? For instance, if the seizures were customarily precipitated by drugs or hypoglycemia, would the electroencephalograms have been more abnormal than if the seizures were not dependent on any known physiologic stress or intoxication of the nervous system?

At the Boston Psychopathic Hospital, my associates and I recently analyzed cases of seizures due to rum intoxication, selecting only patients whose seizures were entirely dependent on alcoholic overindulgence and who never had seizures prior to the onset of heavy drinking and did not have a family history of fits or convulsions. The electroencephalograms were surprisingly normal.

We have also seen 2 or 3 cases of seizures occurring in the acute withdrawal phase of barbiturate poisoning. The electroencephalograms were normal.

The problem as to whether the clinical findings correlate with the electroencephalographic abnormality always implies the converse, whether the electroencephalographic abnormality correlates well with clinical findings. If a patient has an abnormal electroencephalogram, does that signify he is more likely to have epilepsy now or later? From my work with Dr. S. Levin in cases of neurosyphilis, I am convinced that the more abnormal the electroencephalogram, the greater the chance of finding seizure-like phenomena in the histories of patients with neurosyphilis.

DR. JOHN ABBOTT: Dr. Cobb has asked whether the larger amount of medicine taken by patients with abnormal electroencephalograms might increase the abnormality of the tracing. The answer would appear to be "No." Goldman and Schwab concluded, from independent studies, that patients to whom anticonvulsants were administered showed improvement in the epilepsy and in the electroencephalogram

pari passu with the passage of time. Lennox and Gibbs showed that the electroencephalographic pattern improved immediately with appropriate intravenous doses of certain anticonvulsants.

Dr. Cobb also observes correctly that among patients with normal electroencephalograms fits in infancy should hardly be called "rare" but can be described, at least for this series, as rarer than among patients with abnormal electroencephalograms. That is, with respect to fits in infancy the two groups of patients overlap, and there is a difference in favor of the group with normal electroencephalograms. This overlapping of the two groups, with a difference in favor of the group with a normal electroencephalogram, was a feature of almost every comparison of the two groups.

Dr. Cobb asks about the indications for withdrawal of medication. That so many patients (7 of 40) with normal electroencephalograms had stopped medication came as a pleasant last minute surprise, and there has not yet been time to analyze these 7 cases in detail. It is to be hoped that from this analysis, which is to be undertaken, there will emerge criteria other than the occurrence of a normal electroencephalogram which will have prognostic value with respect to the withdrawal of anticonvulsants.

As an intelligence test, the presentation of the first slide was too hurried to be fair, and those who failed the test need not feel embarrassed. This slide showed the age at the time of electroencephalographic recording for each of the 40 patients with normal patterns and for each of 38 patients with abnormal patterns. The group of 38 patients was constructed by seeking for every patient who at a certain age had a normal electroencephalogram a corresponding patient who at the same, or nearly the same, age gave an abnormal record. For every patient who gave an abnormal pattern at the age of 35 or less, it was possible to find a patient who had given an abnormal electroencephalogram at the same age. For patients between the ages of 36 and 72, this exact matching was not possible, but the average age was the same for patients in this age range who gave normal and for patients who gave abnormal electroencephalograms. For the 2 oldsters who had normal electroencephalograms at 73 and 75 years of age, respectively, there could be found no corresponding patients who gave abnormal electroencephalograms at even approximately these ages; hence, in the selected group of patients with abnormal electroencephalograms there are only 38 patients, or 2 less than the group of 40 patients with normal electroencephalograms. This matching, simple in fact but complicated in description, was undertaken in order to correct for factors due to age differences between patients with normal and patients with abnormal electroencephalograms.

Dr. Lennox asks about the criteria used in classifying records as normal or abnormal. Briefly, they were as follows: (1) symmetry, as against asymmetry; (2) a predominance of activity faster than 8 per second, as against activity slower than 8 per second; (3) absence, as against presence, of paroxysmal runs of any but normal alpha activity; (4) absence, as against presence, of single waves slower than 8 per second and higher in voltage than the predominant 8 per second or faster activity; (5) freedom from disturbance, as against slowing, during the first or second minute of overbreathing in a nonfasting state.

It is reassuring to learn that Dr. Lennox found normal electroencephalograms among 25 per cent of the epileptic patients studied in his private laboratory. It is a familiar fact that the incidence of abnormal electroencephalograms varies immensely with the "normality" of samples from the normal population, and one might well expect such variation in samples from the epileptic population. When, in 1941 or 1942, my colleagues and I first got normal electroencephalograms in about 20 per cent of epileptic patients, at a time that others were reporting 16 per

cent or less, we were disconcerted and decided to start all over again. This paper has been a product of our second start, and we find ourselves now in the best of company. Our head technician is a Scotchwoman, and she approves of our findings, so that even the factor of Scottish descent in recording and interpretation has been allowed for.

As to the factor of age, about which Dr. Lennox speaks, I hope that the more detailed account of the first slide just given will meet some of his valid criticism.

With respect to differences between the two groups on the basis of the types of seizures, notably petit mal as opposed to grand mal, some answer to Dr. Lennox' again valid criticisms may follow from a review of the slide showing analyses of the two groups for types of seizures. In each group the percentages of patients presenting petit mal and those presenting grand mal seizures were about the same. However, 30 per cent of the group with normal electroencephalograms had grand mal alone, without any other type of seizure, and only 15 per cent of those with abnormal records had grand mal alone. This still leaves open the possibility that the higher frequency of seizures among patients with abnormal electroencephalograms may be due to the greater prominence of petit mal seizures among such patients. Dr. Lennox' comments in this connection point the direction for further investigation.

In answer to Dr. Lennox' question about prognosis, it would appear from this study that a normal record between seizures is prognostically favorable, but only "favorable." It does not preclude occasional seizures despite the most liberal exhibition of anticonvulsant drugs.

Dr. Greenblatt asks about external precipitants of seizures and the relation of vulnerability to such precipitants and the character of the brain wave record. This question also points the direction for further study. In the work of other investigators there is much to indicate that the patient with an abnormal electroencephalogram is more vulnerable to the factors which may cause seizures than is the patient with a normal electroencephalogram. But this study, at least as far as it has been carried, does not contribute an answer to this interesting question.

Methylphenylethyl Hydantoin ("Mesantoin") and Trimethadione ("Tridione") in Treatment of Epilepsy. DR. HARRY L. KOZOL and DR. WILLIAM G. LENNOX.

Tetraethyl Lead Poisoning: Delirium-Tremens-Like Psychoses with Encephaloneuropathy. DR. LEO ALEXANDER.

This paper will be published in full elsewhere.

NORTHERN CALIFORNIA SOCIETY OF NEUROLOGY AND PSYCHIATRY

George Johnson, M.D., *President, in the Chair*
Regular Meeting, Dec. 5, 1946

Phenomena of Sensory Extinction. DR. NORMAN REIDER, San Francisco.

This paper was published in full in the June 1946 issue of the ARCHIVES, pages 583-590.

DISCUSSION

DR. CHARLES D. ARING, Cincinnati: It has been taught that the neurologic examination consists essentially in comparison of the form and functions of one

side of the body with those of the other, and of the functions of the patient with those of the examiner. It seems that to this definition it must now be added that simultaneous testing of the two sides may be necessary. The phenomenon of extinction or suppression requires further refinement of the local technic of neurologic examination. The point made by Dr. Reider that the manifestations of extinction will be missed unless double sensory testing is practiced is now obvious.

This factor in the sphere of vision was first called to my attention about twelve years ago by Dr. Gordon Holmes in the wards of the National Hospital, London, when he demonstrated what may now be termed suppression or extinction; then it was called visual inattention. It was thought to represent lack of attention or concentration, and possibly to be due to a lesion of the frontal lobe or, as I recall, to minute or early lesions in the neighborhood of the visual fibers. As has been reported by Dr. Reider, further studies have revealed that extinction may affect any sensation.

It is interesting that one cannot get some evidence in the matter with the electroencephalographic technic if, as Dr. Reider believes, the phenomenon is related to the extinction phenomenon of Dusser de Barenne. I do not believe that a tantalum plate in the skull would make any difference in this regard, since it has been shown that one may record quite satisfactorily through them. I wonder whether there is any relation between handedness and extinction?

I myself have increasingly been able to demonstrate extinction to the satisfaction of students and house officers in patients with cerebral lesions, an experience which I am sure will be universal when the technic of simultaneous or double sensory stimulation comes to be more generally used in the neurologic examination.

Dr. Meyer A. Zeligs, San Francisco: One might comment briefly on the nature of the causalgic phenomenon associated with irritation of homologous areas in the opposite extremity, which Dr. Reider described. I do not know whether or not Dr. Reider or Dr. Bender was able to demonstrate the phenomena of sensory extinction with disease of the spinal cord.

Livingston's theories (Pain Mechanisms: A Physiological Interpretation of Causalgia and Its Related States, New York, The Macmillan Company, 1943) are helpful in understanding irritation in homologous areas on the two sides of the body —why persons with causalgia, when faced with a noxious stimulus, not only have pain in the affected area but also may have it in the opposite extremity.

Livingston expressed the belief that in the causalgic state there is a constant bombardment of pain impulses coming in through sympathetic pathways at a spinal level, setting up an irritative state in the "internuncial pool" of neurons at that level. He stated the belief that the explanation of causalgia, and of causalgic phenomena in homologous areas, is this irritation of the internuncial pool, which extends both contralaterally and horizontally. Persistent noxious stimuli passing through this internuncial system produce a "reflex dystrophic state," which may cause a similar disturbance on the opposite side. I think such a neural mechanism probably represents an entirely different phenomenon from that which Dr. Reider has described, but it may be of value in helping to understand sensory extinction phenomena in the cortex.

Dr. Ephraim Roseman, Louisville, Ky.: Apparently, this extinction phenomenon, which I prefer to think of as a suppressor phenomenon, is an effect of stimulation. The examiner has to stimulate one side all the time. It would seem to me that this study is good clinical correlation of the work of Dusser de Barenne and McCulloch (Dusser de Barenne, J. G., and McCulloch, W. S.: *J. Neurophysiol.* **4**:311, 1941. Dusser de Barenne, J. G.; Garol, H. W., and McCulloch, W. S.

ibid. **4**:324, 1941) in monkeys and chimpanzees, in which they identified definite suppressor areas, e. g., areas 2S, 4S, 8S and 19S. By stimulation of these areas they obtained the suppressor phenomenon, and the electroencephalogram showed waves which decreased in amplitude, beginning closest to stimulated areas and then spreading. Sometimes it would take a few seconds for this wave of electrical suppression to spread; at other times, a little longer. Stimulation was either with strychnine or with electric current. These areas can be defined histologically as Bailey has shown. It seems that Dr. Reider's material may be correlated with experimental observations.

I should like to ask whether Dr. Reider knows of any case in which the suppressor phenomenon occurred without preexisting history of sensory loss or defect of the visual fields. Such an occurrence would be clinical evidence corroborating the work of Dusser de Barenne and McCulloch.

Dr. Norman Reider, San Francisco: I do not know the correlation between handedness and this phenomenon. It is true that most injuries have been on the right side of the brain in the cases reported to date. It would be immeasurably more difficult to demonstrate suppression in cases of damage to the left side of the brain because of speech deficit.

Dr. Zeligs has cited Livingston's theory of the spread of causalgic pain. The phenomenon that occurs with injury of the nerve root or the peripheral nerve is an intensification of sensation in the causalgic syndrome, rather than the obscuration of suppression or extinction. Bender has stated the belief that extinction and intensification belong in the same general category of behavior.

I made brief reference to Dr. Roseman's question when I said that I suspected strongly that if the phenomenon of obscuration is found it may be considered as evidence of prior, severer, damage than that which the patient shows at the time of examination. I have no evidence of the phenomenon having occurred without previous damage, but theoretically it should be possible.

Book Reviews

Fundamentals of Clinical Neurology. By H. Houston Merritt, M.D.; Fred A. Mettler, M.D., and Tracy Jackson Putnam, M.D. Price, $6. Pp. 289, with 96 figures and 8 tables. Philadelphia: The Blakiston Company, 1947.

This volume is different from most works on neurology in that it is packed with anatomic facts, illustrated by many diagrams, but deficient in graphic clinical descriptions that make the subject come alive. The material would probably be better termed applied neuroanatomy. The descriptions are terse and require of the reader a considerable power of visualization of the nervous system in its three dimensional aspect. A great many anatomic minutiae are introduced, the majority of which are based on patient studies of the hodology of the nervous system, but which are not known to have anything in the way of clinical expression. This makes for hard reading and harder remembering. Neurology is a complex subject, but this work, in emphasizing the complexities, tends to make it almost discouraging, however far this may be from the authors' intention.

The first part is a brief discussion of the clinical means and physical diagnosis of neurology. Much of the detail of the history taking and physical examination, which is recorded in many texts and which the practitioner should already know, has purposely been left out. Burdensome and lengthy descriptions of variations of reflexes and occult signs—usually more confusing than edifying—have been avoided.

The second part, about five sixths of the text, is neuroanatomy as related to the syndromes one meets in the clinic. Treatment is mentioned only briefly. Systematically, each level of the peripheral and central nervous systems is treated. Diagrams, illustrations and charts are profuse and used well, making for easy and quick reference. The verbiage, moreover, is reduced. In general, controversial issues are avoided. The diagrams of the thalamic nuclei and their cortical connections (chapter 13), however, are included more for the benefit of the experienced neurologist than that of the practitioner, especially since specific localized function of the thalamus is not discussed. The chapter on the cerebrospinal fluid is well worth the space allotted to it. The clinical aspect of the autonomic nervous system has been almost completely neglected.

The value of this book lies in its emphasis on the deductive method of diagnosis —the anatomic basis of neurology. Surely, the practitioner cannot help but acquire a wholesome, scientific approach to neurologic problems from this text as a foundation. It would be worth while to dissect a brain as one reads the text.

CORRECTION

In the April 1947 issue of the ARCHIVES (**57**:481, 1947), the address of Drs. Wilder Penfield and William Feindel was given as Toronto, Ontario, Canada. Both authors are in Montreal, Canada.